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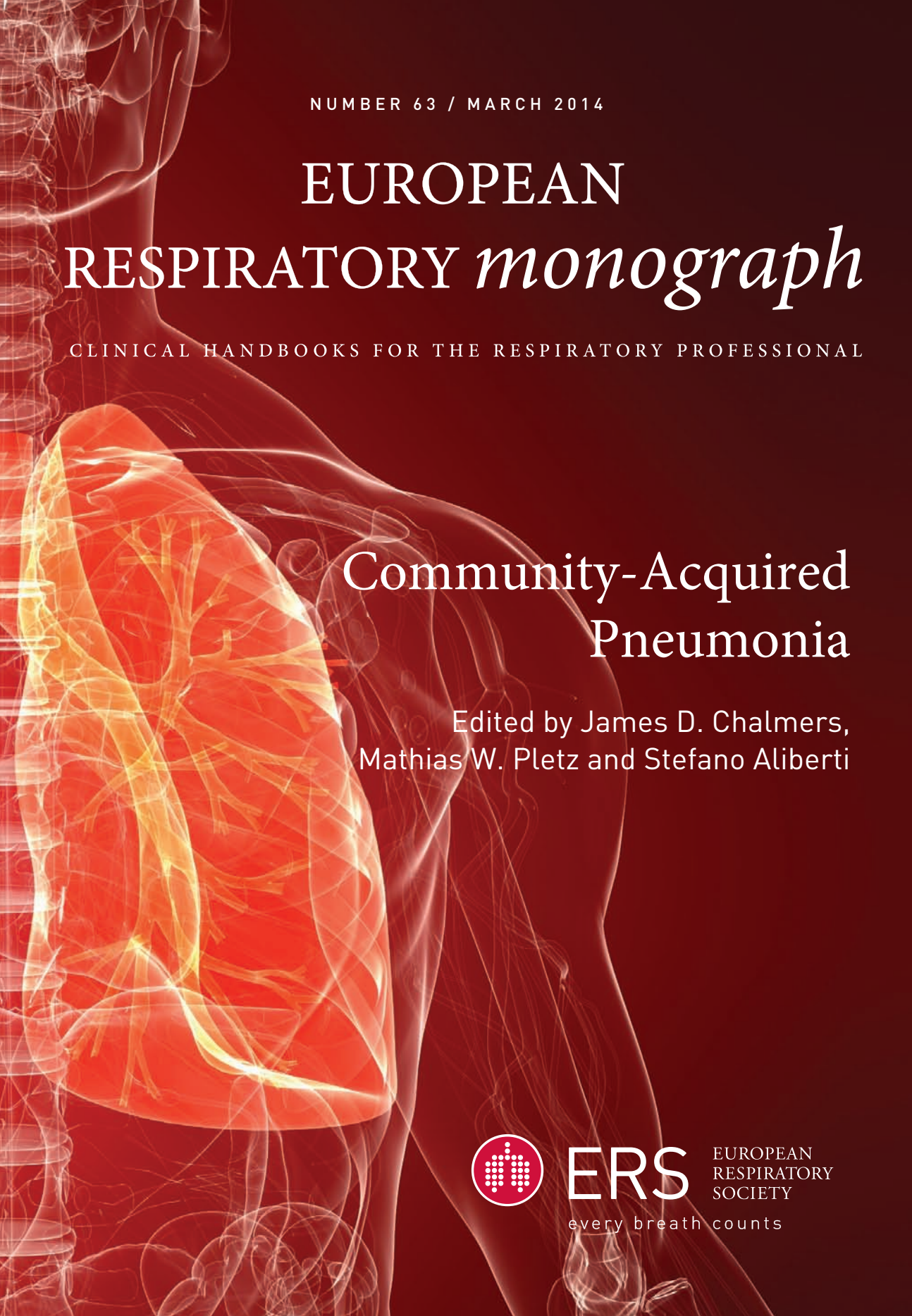

Community-Acquired Pneumonia

Edited by James D. Chalmers, Mathias W. Pletz and Stefano Aliberti

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Community-Acquired Pneumonia

Edited by
James D. Chalmers, Mathias W. Pletz and Stefano Aliberti

Editor in Chief
Tobias Welte

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This book is one in a series of *European Respiratory Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Preface

Tobias Welte
Editor in Chief

Community-acquired pneumonia (CAP) is the leading cause of death due to infectious disease worldwide. As the incidence of CAP increases with increasing age, the number of cases of pneumonia is increasing steadily, in parallel with changes in demography. In recent years, we have learned a lot, primarily from data from large multicentre networks in Spain, the UK, Germany and the USA, about the course of this disease, its complications, risk factors for increased mortality and the effectiveness of various antibiotics. In addition, the understanding of the pathogenic mechanisms of bacteria and the role of pathogen–host interaction has improved considerably.

Despite the enormous progress in the understanding of CAP, the hospital mortality rate is as high as it was 50 years ago. Unlike hospital-acquired pneumonia, however, an increasing development of resistance of the most important respiratory pathogens does not play a significant role. The key factor for the increased mortality is, along with the rising age and the increased number of comorbidities of the patients, the virulence of the pathogens. The introduction of antibiotic therapy in the 1940s has meant that pathogens are reliably killed, reducing the mortality rate dramatically. However, the increase of pathogenic factors caused by destroying the pathogen or late onset of effective therapy has not been successfully tackled to date.

The future of the treatment of CAP is, therefore, not related to the improvement of diagnostics or the development of new antibiotics. Instead, it will focus on two other fields: prevention and immune modulation. Vaccines as an essential preventive measure are already available for some pathogens, but their further development, in particular to improve immunogenicity in the elderly, is a major subject of research. Modulation of the immune response, both to limit overshooting reactions as well as to improve lack of immune response, has not been successful despite many different attempts in the past. Due to the rapid development of sequencing technology, it will be possible to determine risk profiles of patients quickly and this will allow individualised therapy according to the immune status of the patient. This is the music of the future, although a new form of anti-infective therapy, including pharmacokinetic considerations and a risk stratification approach, stands out already on the horizon.

I want to thank the three guest editors, James Chalmers, Mathias Pletz and Stefano Aliberti, for their tremendous work in preparing this issue of the *European Respiratory Monograph* (*ERM*), which summarises the current knowledge about the prevention, diagnosis, risk stratification and therapy of CAP and gives an outlook to the future. The book represents an ideal basis for all clinicians, basic scientists and people operating in this field in the pharmaceutical industry to gain an overview of the state of knowledge. I am convinced that they will find this *ERM* useful for further considerations.

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Guest Editors

James D. Chalmers

James D. Chalmers is a Wellcome Trust Postdoctoral Fellow and Lecturer in Respiratory Medicine at the University of Dundee, UK. He trained in Glasgow and Edinburgh, performing his PhD studies at the Medical Research Council (MRC) Centre for Inflammation Research in Edinburgh investigating the role of innate immunity in non-cystic fibrosis (CF) bronchiectasis. His research and clinical interests are in respiratory infections, particularly community-acquired pneumonia (CAP), bronchiectasis and chronic obstructive pulmonary disease (COPD). He now leads a research group at the University of Dundee investigating the mechanisms of pulmonary bacterial infections, supported by grants from the Wellcome Trust, MRC, Scottish Government and charities.

James Chalmers has been awarded several prestigious young investigator awards, including from the European Respiratory Society (ERS) and British Thoracic Society (BTS). He has published widely on respiratory infections, with over 60 articles in peer reviewed journals since 2008. He is a member of the international advisory board of *The Lancet Respiratory Medicine*. He is heavily involved in international respiratory societies, being a current member of the BTS Science and Research Committee, the ERS Long-Range Planning Committee and the American Thoracic Society Microbiology, Tuberculosis and Pulmonary Infections Program Committee.

Mathias W. Pletz

Mathias W. Pletz, Professor for Infectious Diseases, is a board-certified physician for internal medicine, pulmonology and infectious diseases and the head of the Center for Infectious Diseases and Infection Control of the University Hospital in Jena, Germany. He also leads a clinical research group focusing on novel diagnostic and therapeutic strategies against multidrug-resistant bacterial pathogens, funded by the German Ministry for Science and Education.

Mathias Pletz received his PhD in Virology at the University of Leipzig, Germany. During his thesis he worked as a guest researcher at the Food and Drug Administration Laboratory of Parasitic Pathology and Biochemistry in Bethesda, MD, USA. After his medical training at the University of Leipzig, Baylor College of Medicine (Houston, TX, USA) and the University of Basel (Switzerland), he started his residency at the Chest Hospital in Berlin, Germany. Subsequently, he spent 2 years as a postdoctoral researcher at Emory University (Atlanta, GA, USA), working with Keith Klugman's group on the spread of multi-resistant pneumococci. In addition he served as a guest researcher at the Centers for Disease Control and Prevention (CDC) in Atlanta, exploring the severe acute respiratory syndrome (SARS) epidemics.

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After his return to Germany, he finished his medical training at the Dept of Respiratory Medicine at the Hannover Medical School.

Mathias Pletz is the deputy director of the German Competence Network for Community-Acquired Pneumonia (CAPNETZ), a member of the board of directors of the German-Austrian-Swiss Paul-Ehrlich-Society for antimicrobial chemotherapy, and scientific advisor for the German Robert Koch Institute. He has published more than 100 papers on pneumonia, pneumococcal vaccines, respiratory infections, antimicrobial resistance and pharmacokinetics of antibiotics in the critically ill. He has also received numerous scientific awards, *e.g.* the Honor Award Certificate from the CDC, the Kass-Award of the Infectious Diseases Society of America and the Respiratory Infections Awards from the ERS.

Stefano Aliberti

Stefano Aliberti is Assistant Professor in Respiratory Medicine at the University of Milan-Bicocca, Milan, Italy, and consultant at the San Gerardo Hospital in Monza, Italy. He trained at the Institute of Respiratory Diseases at the University of Milan, under the mentorship of Professor Francesco Blasi. During his fellowship, he received research grants to investigate the epidemiology of non-CF bronchiectasis and COPD, and he worked as a visiting research fellow at the Division of Infectious Diseases at the University of Louisville, KY, USA. He has been an active member of the Community-Acquired Pneumonia Organization (CAPO) international study group since 2006, and a member of the Community-Acquired Pneumonia Inflammatory Study Group (CAPISG). His research and clinical interests are in both acute and chronic respiratory infections, including CAP, non-CF bronchiectasis and atypical mycobacteria. He was awarded the young researcher award in respiratory infections from the ERS in 2007. During the past 10 years, he has been involved in several clinical and translational studies on these topics at both national and international level. Stefano Aliberti has published over 60 articles on CAP in peer-reviewed journals since 2006. He is associate editor of *Breathe* and the *European Journal of Internal Medicine*. He has been heavily involved in the ERS, as Secretary of the Respiratory Infection Group and Secretary of the Assembly of Respiratory Infections.

Introduction

James D. Chalmers[*], *Mathias W. Pletz*[#] *and Stefano Aliberti*[¶]

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The morbidity and mortality of respiratory tract infections in Europe throughout history is incalculable, but when the English writer John Bunyan coined the phrase ''Captain of all these men of death'' to describe tuberculosis (TB) in 1680, TB was estimated to cause 15–20% of all deaths in Europe. It was hard to imagine at that time that another infection might one day take this crown. In 1918, the father of modern medicine, Sir William Osler, observed that pneumonia had overtaken TB as one of the leading causes of death in Europe and described pneumonia as the ''Captain of the men of death'', an appellation it still justifies today.

While improvements in public health and sanitation reduced mortality from many, mostly food-borne, infections, it was not until the widespread introduction of antibiotics after the Second World War that mortality from pneumonia in Europe began to fall significantly. Since then, there have been few new treatments and limited progress in reducing mortality from pneumonia. While mortality rates for cardiovascular diseases and many cancers are falling in Europe, the rates for hospitalisation and deaths from pneumonia are static or rising. This is a disease of huge clinical and public health importance.

It is for this reason we are delighted to introduce the 63rd issue of the *European Respiratory Monograph* (*ERM*), dedicated to the epidemiology, pathophysiology, microbiology, investigation, management and prevention of community-acquired pneumonia (CAP). The 20 chapters of this *ERM* serve as a comprehensive text, describing the modern approach to this disease, each chapter written by internationally recognised experts in their field. Major changes in our understanding and management of pneumonia have been emphasised, including the new microbiology techniques that are set to change how we detect and diagnose infection, the emerging role of anti-inflammatory therapies and the current controversy over inhaled corticosteroids as a cause of pneumonia in patients with chronic obstructive pulmonary disease. The changing face of pneumonia reflects the world around us, with an increasing impact of antibiotic resistance and an ageing population with comorbidities to the fore. We now recognise the important impact of this disease on long-term outcomes. Previously regarded as a purely ''acute'' condition, new evidence shows that pneumonia can destabilise the precarious balance in patients with comorbidities and poor performance status, even after apparent recovery from the acute episode.

This is a broad and multidisciplinary book, covering diverse specialities from epidemiology to the basic science of pneumococcal infection, and reviewing CAP in children, in primary care and in the intensive care unit.

As much as in any other disease, CAP requires improvements in clinical care and to achieve progress through innovative research. Every clinician in every speciality will encounter pneumonia in their daily practice and we hope that this *ERM* will serve as a complete and up-to-date reference for our colleagues.

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Chapter 1

Epidemiology of CAP in Europe

Anika Singanayagam[*], *James D. Chalmers*[#] *and Tobias Welte*[¶]

SUMMARY: This article describes the epidemiology of community-acquired pneumonia (CAP) in Europe. Lower respiratory tract infections are the fifth leading cause of death worldwide with the bulk of the mortality attributable to CAP. Pneumonia disproportionately affects elderly populations and demographic changes within Europe are leading to an older, more comorbid population at high risk of pneumonia. Consequently, recent data suggests a progressive rise in hospitalisations for pneumonia throughout Europe over the past 10 years.

CAP places a substantial burden on healthcare with costs largely attributable to inpatient care. Antibiotic resistance, particularly *Streptococcus pneumoniae* resistance to penicillin and macrolides, is rapidly increasing in Europe and poses a serious threat to future effective treatment. Prevention of pneumonia requires an understanding of the population risk factors, which will be discussed in this chapter.

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In Europe, community-acquired pneumonia (CAP) is the leading infectious cause of death and constitutes a considerable economic burden on healthcare systems [1]. Lower respiratory tract infections (LRTI) were ranked as the fifth most common cause of death across the World Health Organization (WHO) European region in the 2010 Global Burden of Disease Study [2] and accounted for 0.23 million (2.3%) deaths and 2.2 million (1.5%) disability adjusted life years in Europe [3]. CAP disproportionately affects the elderly population's mortality and morbidity rates, with increased incidence. With the projected proportion of people aged $\geqslant$65 years increasing to a third of the population over the next decade from a sixth of the population in 2004 (based on current trends) [4], the impact of CAP is set to become greater and more costly.

Incidence of CAP in Europe

The incidence of a disease measures the number or rate of new cases of disease that occurs in a population over a specified time period. Difficulties arise when evaluating European incidence rates for CAP, as study populations and calculation methods differ across published studies [1]. Across Europe, only Spain, Finland and the UK have precise epidemiological data on CAP [5].

Among the difficulties in determining the incidence of CAP, the majority of cases are managed as outpatients where chest radiograph confirmation is not sought. Use of International Classification

of Disease (ICD) codes of hospital discharges are used in many diseases to determine the incidence, but there is no specific ICD-10 code for CAP and, therefore, population data based on these codes reflect a mix of CAP and other LRTIs [6]. Microbiological diagnosis is often unavailable due to lack of sputum for culture or prior use of antibiotics. Therefore, the burden of CAP may be underestimated because of the differences in CAP definition and clinical heterogeneity.

Allowing for these limitations the reported annual incidence rate of CAP in adults across Europe range between 1.07 and 1.2 per 1000 person years and 1.54 and 1.7 per 1000 population [1].

Age, sex and comorbid conditions

The incidence of CAP in Europe varies by age, sex and level of underlying comorbidity. CAP incidence increase with age and the presence of comorbidity, and is higher in males than females [6]. Incidence rate in a population-based cohort study of 11 241 patients aged $\geqslant$65 years in Spain was 14 per 1000 person years (10.5 for hospitalised and 3.5 for outpatient cases) [7]. In a Finnish study, a six-fold increase in incidence between the ages of 30–44 years and $\geqslant$75 years was reported [8]. Age-specific incidence of hospitalisation from a UK study was 7% higher for males than females [9]. The male predominance for hospitalisation with CAP has also been shown in a German study (3.21 per 1000 people per years in males *versus* 2.52 per 1000 people per years in females) [10], and a Danish study of 48 551 individuals aged 50–64 years (4.2 per 1000 person years in males *versus* 3.4 per 1000 person years in females) [11].

CAP incidence rates are also higher in persons with underlying comorbid conditions. Incidence rates as high as 22.4 (95% CI 21.7–23.2) per 1000 person years were depicted in a cohort of chronic obstructive pulmonary disease (COPD) patients [12]. Patients with COPD make up between a quarter and a third of most hospitalised cohorts with CAP, reflecting the high frequency of the disease in COPD patients [13–15]. High incidence rates have also been reported in the immuno-compromised (almost three-fold higher than in immunocompetent subjects) [16], including: Spanish patients with rheumatic diseases treated with tumour necrosis factor antagonists (5.97 (95% CI 4.87–7.25) per 1000 person years) [17]; long-term corticosteroid therapy (40.1 per 1000 person years) [16]; and a French study of patients with HIV (12.0 (95% CI 9.9–14.0) per 1000 person years) [18].

Incidence in community settings

Estimates suggest that 50–80% of CAP cases will be managed in the community. In community settings in Europe, CAP incidence range between 1.7 and 11.6 cases per 1000 person years in adults [4]. In the European Union (EU), approximately 3 370 000 ambulatory cases are expected annually. The mean number of healthcare visits per patient in a 2-year population-based study of CAP in Spain was 4.5, with 72% in the primary care setting [17]. Whilst most CAP patients are treated in community settings, the majority of reported CAP studies are on hospitalised patients and so the true burden of community-based disease is probably underestimated due to the lack of data (table 1). A recent study from the Netherlands that used administrative data suggested that only 2.3% of cases were referred to hospital, indicating that the vast majority of suspected pneumonias are treated in the community [19].

Incidence in hospital settings

Hospital admission rates for CAP vary significantly between European countries, ranging from 20% to 50%, with approximately 1 million hospital admissions for CAP per year expected in the EU (fig. 1) [4].

Hospitalisation is associated with older age, the presence of comorbid conditions and greater severity of illness [20–22]. Major efforts have been devoted over the past 20 years to increase the

Table 1. Pneumonia outpatient incidence in Europe

Country	Study period	Age years	Cases per 1000 population		
			Male	Female	Male and female
Finland	1981–1982	15–29	4.2	4.6	
		30–44	5.6	5.9	
		45–59	9.8	7.0	
		60–74	25.0	9.0	
		>75	65.2	19.6	
		⩾60	33.0	11.8	
Spain	1993–1995	15–39	1.2	1.0	
		40–64	1.8	1.4	
		>64	5.2	1.9	
		All ages			1.6
	1999–2001	15–44	0.8	0.6	
		45–64	1.4	0.7	
		65–74	3.2	1.6	
		⩾75	8.7	3.0	
		All ages	1.6	0.9	
	2002–2005	65–74	3.0	2.2	
		75–84	5.3	2.8	
		⩾85	10.0	7.9	
		All ages	4.2	2.9	
Italy	1999–2000	15–44			0.9
		45–64			1.6
		>64			3.3
		All ages	1.7	1.7	
Germany	2003	>18			8.7

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proportion of patients with pneumonia managed in the community, with the associated reduced risk of hospital-acquired infections and costs associated with hospitalisation.

However, there is evidence that hospital admissions for pneumonia are now rising. A sharply increasing trend in pneumonia hospitalisations was depicted in a UK study between 1997–1998 and 2004–2005 [9]. In this study, using UK National Health Service hospital episode statistics, age-standardised incidence of hospitalisation with pneumonia was shown to increase by 34% from 1.48 to 1.98 per 1000 persons between 1997–1998 and 2004–2005. The increase seen was most striking in older adults. Data from a German study that reviewed the inpatient records of all hospitalised patients with CAP in 2005–2006 (total 388 406 patients) showed that CAP incidence increased from 2.75 per 1000 people per year in 2005 to 2.96 per 1000 people per year in 2006 [10]. Again, they showed that incidence strongly correlated with age, and the incidence in patients aged ⩾60 years was 7.65 per 1000 people per year [10]. Increases in hospital admissions for pneumonia have also been noted in a large Danish cohort study (2.8 per 1000 person years to 4.4 per 1000 person years between 1994 and 2003) [23]. In a study of adult hospital admissions in Portugal between 2000 and 2009 including 294 027 admissions for pneumonia, there was a 28.2% increase in the annual average rate of hospital admissions for pneumonia per 1000 population. In this study the average age of patients also increased by 5% between 2000 and 2009 [24].

Therefore, there is a consistent increase in the incidence of CAP across Europe. Although many of these studies speculate on possible reasons for the increases, the precise underlying cause has not been identified [9]. Possible explanations include demographic changes that result in many more multimorbid elderly patients surviving to an older age [25]. Increasing use of immunosuppressive therapies and changes in the way in which patients access primary care and hospital services have also been considered. This is clearly an area requiring further research.

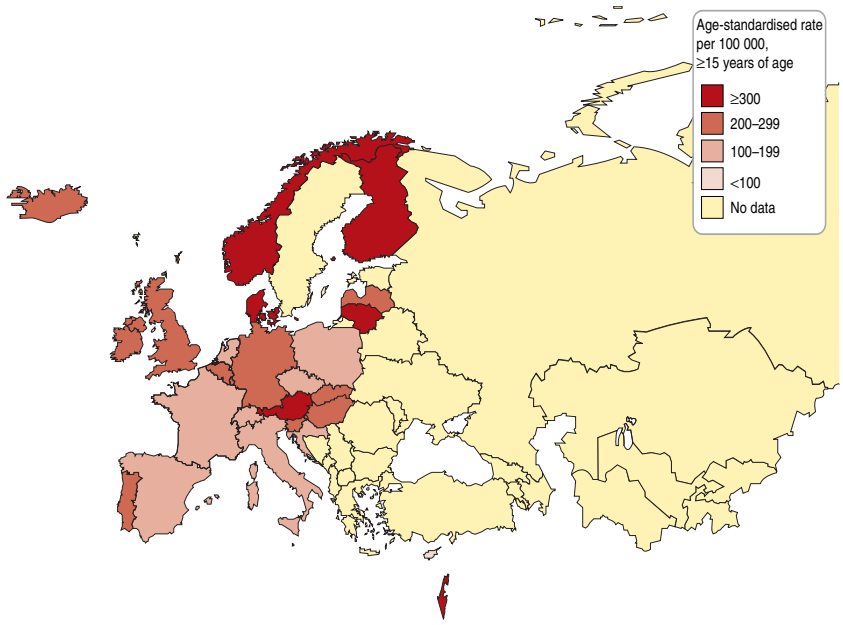

Figure 1. Hospital admission rate for pneumonia in adults. Reproduced from [4].

Risk factors for CAP in adults

Population-based studies have identified a large number of risk factors for pneumonia in adults that were recently consolidated in a systematic review [1]. The major identified lifestyle risk factors included: current or former cigarette smoking, alcohol consumption greater than 40 g·day^{-1}, and low body mass index [1]. Regular contact with children appears to be a risk factor (reported odds ratio 1.48, 95% CI 1.26–1.75) [26]. It is speculated that this is because children act as a reservoir of pneumococcal carriage, which can be transmitted to adults and cause pneumonia. However, data from countries in which 7-valent pneumococcal vaccination (and later 13-valent pneumococcal vaccination) for children has been introduced during the last decade, showed that in addition to the decrease in the incidence of invasive pneumococcal disease in children a remarkable effect in adults was also demonstrated [27].

Comorbidities are associated with pneumonia as mentioned previously. Along with COPD, which is one of the strongest risk factors for pneumonia, that increases the risk from two- to four-fold, cardiovascular disease, heart failure, diabetes, liver disease and cancer are all associated with increased risk [1]. 10–20% of hospitalised CAP patients have risk factors for aspiration [28] and population-based studies reflect this, in that disorders associated with impaired swallowing or consciousness are heavily associated with population risk of CAP. These include epilepsy, Parkinson's disease, multiple sclerosis, dysphagia and stroke [1, 29].

Medications may increase the risk of CAP. The relationship between inhaled corticosteroids and pneumonia risk is topical [30] and is discussed further in the chapter by Calverley [31]. Most drugs that cause immunosuppression are linked to CAP. In addition, a number of studies have linked gastric acid-suppressing medication, particularly proton-pump inhibitors, with an increased risk of CAP [32] although a recent analysis has cast doubt on this association and the proposed risk is relatively small [33].

Clinical outcomes in CAP: morbidity and mortality

Mortality from CAP in European adults varies widely from country to country [5]. Mortality data is difficult to compare and a comprehensive European wide assessment is lacking.

Age-standardised mortality rates in adults in European countries ranges from 4.5 to 5 per 100 000 in Turkey and Georgia to 30 to 35 per 100 000 in Portugal and the UK, up to 38.28 per 100 000 in Slovakia [4]. Mortality figures range from <1% for outpatients, 5–15% for hospitalised patients, and to more than 40% in intensive care unit (ICU) patients [34]. ICU admission criteria for patients with pneumonia also differs between European countries, with reported admission rates ranging from <5% in Italy to over 10% in Belgium (fig. 2) [4]. In general ICU admission rates in Europe are lower than in the USA, and inpatient mortality rates appear similar [35, 36]. It appears that the majority of patients in Europe who die from pneumonia do so outside of an ICU environment [37].

Age and mortality from CAP

The risk of death from CAP in adults is linked to increasing age. Case fatality rates have been shown to increase with age in several European studies including ones from Finland [8], Portugal [36] and the UK [9]. With the increasingly ageing population in developed countries, the burden of CAP will be felt even more intensely in decades to come. Other variables associated with mortality in CAP are considered in more detail in the chapter by SINTES *et al.* [39], but include female sex, serious underlying comorbidity, recent hospitalisation, use of oral corticosteroids, polymicrobial or bacteraemic pneumonia, multilobar involvement, pleural effusion, ICU admission, impaired alertness, septic shock, acute renal failure and ineffective initial therapy [5].

Aetiology and mortality from CAP

Aetiology is considered in more detail in the chapter by LUNG AND RELLO [40]. Infection with *Streptococcus pneumoniae* has been linked to increasing pneumonia severity and risk of death. In one study, the risk for pneumonia-related mortality was almost three-fold higher if the pneumonia was pneumococcal [41]. However, mortality has not been convincingly linked to pneumococcal antibiotic resistance.

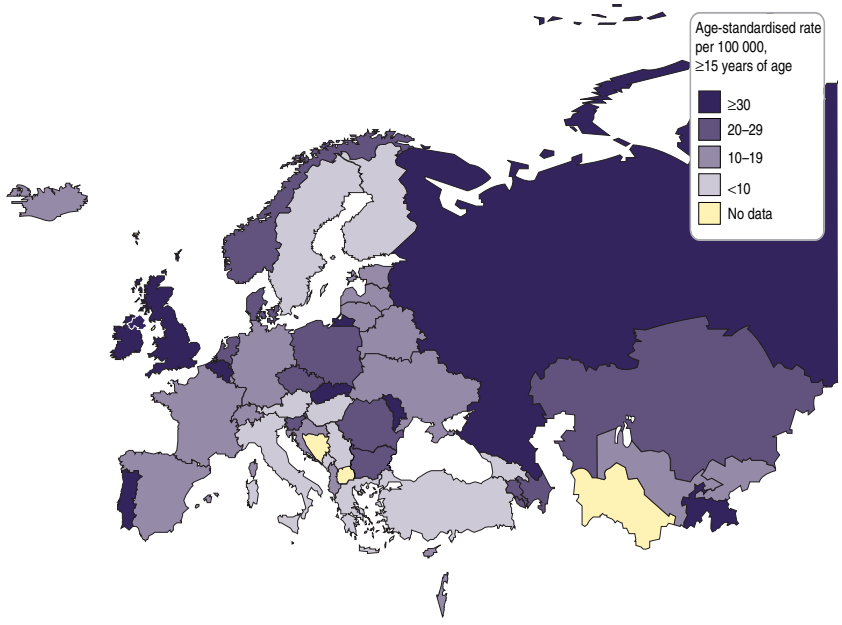

Figure 2. Mortality rate for pneumonia in adults. Reproduced from [4].

Long-term morbidity and mortality from CAP

CAP typically causes symptoms for 3–4 weeks and daily activities may be impaired, on average, for a further 3 weeks. Patients with pneumonia are at an increased risk of morbidity and mortality over the long term even after apparent recovery. Hospital readmission rates are reported between 8% and 46%, constituting significant costs and consumption of medical resources [42]. Mortality rates within 90 days after discharge can be as high as 14% in patients with CAP, and even at 1 year the mortality rates remain higher than that of the general population [3, 43, 44]. CAP is also associated with a significant increase in the risk of cardiovascular events and death from cardiac causes [45]. A long-term population based study from Finland, which followed elderly patients treated for CAP in both outpatient and inpatient settings for a median of 9.2 years, identified a significantly increased risk of long-term and cardiovascular mortality [41].

Morbidity from CAP was assessed in terms of time to return to full activity in one study and varied depending on the infectious aetiology [7]. The longest time to clinical healing and return to daily activities was reported in patients with mixed infections (mixed bacterial and viral (mean $\pm$ SD) 30.0 $\pm$ 19.7 days; viral 23.1 $\pm$ 10.2 days; bacterial 25.0 $\pm$ 18.0 days) [7]. Long-term outcomes of CAP patients in terms of symptom resolution and health-related quality of life (HRQoL) were assessed in a Dutch study. General well-being symptoms recovered more slowly than respiratory symptoms, particularly in patients with underlying comorbidities. 18 months after an episode of CAP, patients had significantly lower scores on physical functioning and general health components of the SF-36 questionnaire than age- and sex-matched controls. Patients with comorbidities had significantly greater HRQoL impairments in physical function, general health, emotional function and vitality than a Dutch reference population [46].

Economic burden of CAP

In Europe, CAP costs are estimated at approximately €10 billion annually, which includes €5.7 billion on inpatient care, €0.5 billion on outpatient care, €0.2 billion on drugs and €3.6 billion of indirect costs from lost working days [4, 5].

Inpatient care costs

Hospital length of stay is a significant cost factor in caring for patients with CAP. In a UK study, median duration of hospital stay for patients with CAP was 4–6 days, compared to a median length of stay of 2 days for all-cause admissions. The length of stay in hospital correlates with increasing age (3 days for patients aged $<$65 years, 6 days if aged 65–74 years, 8 days if aged 75–84 years, and 9 days if aged $\geqslant$85 years ($p<0.001$) [9]. Analysis of hospital discharge data from a Spanish national surveillance system showed that the annual cost of hospitalisation for CAP in Spain was €114.8 million [47]. The care for patients aged $\geqslant$65 years accounted for 58% of this cost. A multicentre observational study from Italy calculated mean healthcare costs per patient per year, including costs during the 6 month follow-up period, as €1586 for an episode of CAP [48]. Similarly, €1553 was the calculated as the mean direct cost for CAP treated patients in a hospital setting in a Spanish study, [49] and €1201 in a German study [50].

Ambulatory care costs

Outpatient care for CAP costs significantly less than inpatient care. A population-based study in Spain estimated that the mean direct cost of treatment for CAP in the ambulatory setting was €196 compared with €1553 in the hospital setting [49].

Aetiology and antibiotic resistance in CAP

S. pneumoniae is the most common cause of CAP in European countries [5]. Whilst a range of organisms are implicated in the aetiology of CAP, the causative pathogen in most cases remains unknown and clinically indistinguishable. Empirical treatment regimens for community-acquired LRTIs must, therefore, be active against pneumococci and continue to evolve to reflect emerging threats from drug resistance.

Before the late 1960s, clinical isolates of *S. pneumoniae* were nearly uniformly susceptible to penicillin. Strains with raised minimum inhibitory concentration (MIC) were first identified in Australia in 1967 before becoming prevalent in South Africa and Spain in the 1970s, and eventually spreading across Europe then globally in the 1990s [51]. Furthermore, resistance to other classes of antimicrobials began to increase including the presence of multidrug-resistant (MDR) pneumococci.

The effect of *in vitro* penicillin resistance on clinical outcome is less well characterised for pneumococcal pneumonia than otitis media or meningitis, and remains a subject for debate. Clinical studies on pneumococcal pneumonia have shown that penicillin MIC $\leqslant 2$ μg mL^{-1} is not independently associated with increased mortality [52–55], and potentially MICs up to 4 μg mL^{-1} can be adequately treated [56]. Investigating the clinical impact of antimicrobial resistance in pneumococcal pneumonia is challenging. Epidemiological analyses of observational data are associated with inherent methodological issues, and controlled trials are difficult to perform. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidance [57] recommends increasing doses of intravenous benzylpenicillin, for strains with MICs up to and equal to 2 μg mL^{-1}, as appropriate in order to achieve adequate time above MIC and bacteriological efficacy. Therapeutic failure has been seen with macrolide- [58] and fluoroquinolone- [59] resistant pneumococci.

On average in Europe approximately 11.6% of invasive *S. pneumoniae* isolates were reported as "nonsusceptible" to penicillin, 16.9% to macrolides and 3.9% as "resistant" to penicillin, according to the European Antimicrobial Resistance Surveillance Network (EARS-Net) data from 2012 [60]. However, comparing data between countries across Europe is challenging because of breakpoint disparities in clinical guidelines used by different countries (table 2), as well as variable quality of surveillance systems. Eight countries reported using EUCAST guidance, six countries reported using the Clinical and Laboratory Standards Institute (CLSI) guidance [61], and one country (UK) reported using a mixture of national, EUCAST and CLSI guidance. The guidance used was not stated for 14 countries. Variation also exists on whether clinical breakpoints for meningitis or nonmeningitis were used. Therefore, translating EARS-Net data to clinical relevance in pneumococcal pneumonia needs to be applied with this in mind.

Nonetheless, significant heterogeneity in levels of penicillin resistance is reported between countries in Europe. In general, lower rates of penicillin resistance are reported in northern European countries than southern and eastern countries [60]. Amongst the 28 countries reporting 10 isolates or more in 2012, 22 reported penicillin resistance rates of $\leqslant 5\%$, two reported rates of 5–10% (Italy and Portugal), with higher rates reported from Bulgaria 28.6%, Lithuania 13.5%, Romania 56.5% and Spain 26.7%. As shown in table 2, the differences in the breakpoints used might have influenced inter-country data comparability [60]. Importantly, with regards to CAP, this data provides important information on the epidemiology of resistance across Europe, but does not necessarily reflect the clinical breakpoint (MIC >2 μg mL^{-1}) at which alternative treatments than penicillin may need to be utilised.

10 European countries reported macrolide nonsusceptibility greater than 25% in 2012, including Belgium (25.4%), Croatia (28.6%), France (28.9%), Italy (34.2%), Lithuania (25.7%), Malta (50.0%), Poland (27.3%), Romania (37.2%), Slovakia (27.3%), and Spain (26.4%) [60]. Eight countries reported rates of 10–25%, with rates of $<10\%$ in 10 countries. Macrolide resistance may

Table 2. Differences in breakpoints between clinical guidelines in use across Europe reporting to the European Antimicrobial Resistance Surveillance Network

Clinical guidance	Sensitive MIC μg mL^{-1}	Resistant MIC μg mL^{-1}	Country reporting use
EUCAST			
Non-meningitis	⩽0.06	>2	Finland, Czech Republic
Meningitis	⩽0.06	⩾0.12	
Non-meningitis/meningitis depending on site of infection			Sweden, Slovakia, Poland, Norway, Malta, Hungary
CLSI			
Non-meningitis	⩽2	⩾8	
Meningitis	⩽0.06	⩾0.12	Bulgaria, Lithuania Cyprus, Portugal
Non-meningitis/meningitis depending on site of infection			
Oral	⩽0.06	⩾2	Ireland, Slovenia
Mixed[#]			UK
Not stated			Austria, Belgium, Croatia, Denmark, Estonia, France, Germany, Iceland, Italy, Latvia, Luxembourg, the Netherlands, Romania, Spain

MIC: minimum inhibitory concentration; EUCAST: European Committee on Antimicrobial Susceptibility Testing; CLSI: Clinical and Laboratory Standards Institute. [#]: CLSI/EUCAST/national guidance. Data taken from [60].

be of greater clinical importance and has been shown to be associated with treatment failure in pneumococcal pneumonia [34, 58, 62].

Outpatient antibiotic sales data was shown to correlate with prevalence of penicillin nonsusceptible invasive *S. pneumonia* isolates ($r=0.75$, $p<0.001$) and macrolide resistance correlated with outpatient macrolide sales ($r=0.88$, $p<0.001$) in a study of 19 European countries and the USA [63]. In an EARS-Net study of 11 European countries, correlation between use of β-lactam antibiotics and penicillin nonsusceptibility in invasive *S. pneumoniae* isolates was also identified ($r=0.8$, $p=0.0002$) [64]. Prolonged courses of sub-therapeutic concentrations of antibiotic [65] and inappropriate use of antimicrobials for acute viral respiratory tract illnesses have been attributed to increasing drug resistance in respiratory pathogens [66]. Promoting judicious antimicrobial usage has therefore been suggested as one strategy to limit the emergence and spread of drug resistant pneumococci [34].

Nonsusceptibility is confined to a few serogroups of pneumococci. Penicillin nonsusceptibility is mainly found in serogroups 9, 14, 19, 23 and to a lesser degree in 6; erythromycin nonsusceptibility is in serogroups 1, 14, 19 and to a small degree in 6, 9, and 33. Dual nonsusceptibility is reported in serogroups 6, 9, 14, 19 and 23.

A small number of highly successful clones (6A, 6B, 9V, 14, 19F, 23F) have dominated the worldwide population of antibiotic resistant pneumococci [34]. Dissemination of MDR serotype 6B pneumococci from Spain to Iceland, possibly by nasopharyngeal carriage in the children of returning holidaymakers, was shown in one study. These pneumococci became established in day-care centres in Iceland between 1988 and 1993, causing a rapid increase in drug resistance rates from 1% to 17% [67]. The multiresistant Spanish 23F-1-19F clone has also been shown to have disseminated globally [68, 69].

Given that a limited number of serotypes account for the majority of penicillin and macrolide resistance globally, pneumococcal vaccines targeted at these strains constitute a valuable strategy in combatting drug resistance. Developing effective vaccines against pneumococcus has been difficult because of poor immunogenicity of the bacterial cell surface polysaccharides [34]. The 23-valent polysaccharide vaccine, developed in the 1980s, has been shown to have limited efficacy against

all-cause pneumonia or mortality in a meta-analysis but is effective in preventing invasive pneumococcal disease (IPD) in the elderly and high risk groups [70]. Pneumococcal conjugate vaccines (PCV), with enhanced immunogenicity, have been shown (in the USA) to lead to reduced *S. pneumoniae* carriage and transmission, and an overall reduction in IPD and pneumonia caused by vaccine serotypes in vaccinated and unvaccinated persons (herd protection), including a reduction in drug-resistant *S. pneumoniae* IPD [71, 72]. Replacement serotypes, such as 19A that emerged following the introduction of PCV7, showed high or increasing levels of nonsusceptibility. This resulted in the development of newer vaccines, such as PCV10 and PCV13, with increased serotype coverage. Ongoing close monitoring of pneumococcal serotype epidemiology is clearly required to assess the impact of these vaccines on serotype incidence and antibiotic resistance [71]. Vaccination strategies are discussed in more detail in the chapter by PLETZ AND WELTE [73].

Antibiotic resistance is not limited to pneumococci. Reports from the USA and Asia have reported an increasing frequency of other drug-resistant pathogens in patients with CAP or in patients with pneumonia acquired in the community but with frequent healthcare contacts [74–78]; so called "healthcare-associated pneumonia", which has not been adopted in Europe and will be discussed in more detail in by EWIG [79]. Fortunately (MDR) pathogens remain relatively uncommon in Europe. Most recent estimates put the frequency of MDR bacteria at 0.9–2.4% of isolates, most frequently methicillin-resistant *Staphylococcus aureus* (MRSA) and MDR *Pseudomonas aeruginosa* in studies from the UK, Spain and Italy [80]. The rates of MDR pathogens appear to be higher in Southern Europe compared to Northern Europe, mirroring the frequency of penicillin resistant *S. pneumoniae* [81, 82]. MDR pathogens and MRSA are significantly less frequent in Europe compared to the very high rates recently being reported in CAP populations from the USA and Asia [78].

Conclusions

CAP makes a substantial impact on adults across Europe, in terms of morbidity, mortality, resource consumption and economic costs. Understanding population-based age and sex-specific data on the epidemiology of CAP is important for future preparedness, economic forecasting and planning of resources, such as prevention strategies, antibiotic usage guidance and vaccination programmes. There has been a significant increase in the incidence of CAP in Europe over the past decade, the reasons for which are unclear.

Statement of Interest

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References

1. Torres A, Peetermans WE, Viegi G, *et al.* Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax* 2013; 68: 1057–1065.
2. Lozano R, Naghavi M, Foreman K, *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2095–2128.
3. The burden of lung disease. *In*: Gibson GJ, Loddenkemper R, Sibille Y, *et al*, eds. The European Lung White Book. Respiratory Health and Disease in Europe. Sheffield, European Respiratory Society, 2013; pp. 2–15.
4. Acute lower respiratory infections. *In*: Gibson GJ, Loddenkemper R, Sibille Y, *et al.*, eds. The European Lung White Book. Respiratory Health and Disease in Europe. Sheffield, European Respiratory Society, 2013; pp. 210–223.

5. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax* 2012; 67: 71–79.
6. Guevara RE, Butler JC, Marston BJ, *et al.* Accuracy of ICD-9 CM codes in detecting community-acquired pneumococcal pneumonia for incidence and vaccine efficacy studies. *Am J Epidemiol* 1999; 149: 282–289.
7. Almirall J, Bolíbar I, Vidal J, *et al.* Epidemiology of community-acquired pneumonia in adults: a population-based study. *Eur Respir J* 2000; 15: 757–763.
8. Jokinen C, Heiskanen L, Juvonen H, *et al.* Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. *Am J Epidemiol* 1993; 137: 977–988.
9. Trotter CL, Stuart JM, George R, *et al.* Increasing hospital admissions for pneumonia, England. *Emerg Infect Dis* 2008; 14: 727–733.
10. Ewig S, Birkner N, Strauss R, *et al.* New perspectives on community-acquired pneumonia in 388 406 patients. Results from a nationwide mandatory performance measurement programme in healthcare quality. *Thorax* 2009; 64: 1062–1069.
11. Kornum JB, Nørgaard M, Dethlefsen C, *et al.* Obesity and risk of subsequent hospitalisation with pneumonia. *Eur Respir J* 2010; 36: 1330–1336.
12. Müllerova H, Chigbo C, Hagan GW, *et al.* The natural history of community-acquired pneumonia in COPD patients: a population database analysis. *Respir Med* 2012; 106: 1124–1133.
13. Singanayagam A, Singanayagam A, Chalmers JD. Obesity is associated with improved survival in community-acquired pneumonia. *Eur Respir J* 2013; 42: 180–187.
14. Aliberti S, Di Pasquale M, Zanaboni AM, *et al.* Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. *Clin Infect Dis* 2012; 54: 470–478.
15. Restrepo MI, Mortensen EM, Waterer GW, *et al.* Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. *Eur Respir J* 2009; 1: 153–159.
16. Vila-Corcoles A, Ochoa-Gondar O, Rodriguez-Blanco T, *et al.* Epidemiology of community-acquired pneumonia in older adults: a population-based study. *Respir Med* 2009; 103: 309–316.
17. Pérez-Sola MJ, Torre-Cisneros J, Pérez-Zafrilla B, *et al.* Infections in patients treated with tumor necrosis factor antagonists: incidence, etiology and mortality in the BIOBADASER registry. *Med Clin (Barc)* 2011; 137: 533–540.
18. Bénard A, Mercié P, Alioum A, *et al.* Bacterial pneumonia among HIV-infected patients: decreased risk after tobacco smoking cessation. ANRS CO3 Aquitaine Cohort, 2000-2007. *PLoS One* 2010; 5: e8896.
19. Snijders B, van der Hoek W, Stirbu I, *et al.* General practitioners' contribution to the management of community-acquired pneumonia in the Netherlands: a retrospective analysis of primary care, hospital, and national mortality databases with individual data linkage. *Prim Care Respir J* 2013; 22: 400–405.
20. Choudhury G, Chalmers JD, Mandal P, *et al.* Physician judgement is a crucial adjunct to pneumonia severity scores in low-risk patients. *Eur Respir J* 2011; 38: 643–648.
21. Arnold FW, Ramirez JA, McDonald LC, *et al.* Hospitalization for community-acquired pneumonia: the pneumonia severity index *vs* clinical judgement. *Chest* 2003; 124: 121–124.
22. Chalmers JD, Akram AR, Hill AT. Increasing outpatient treatment of mild community-acquired pneumonia: systematic review and meta-analysis. *Eur Respir J* 2011; 37: 858–564.
23. Thomsen RW, Riis A, Norgaard M, *et al.* Rising incidence and persistently high mortality of hospitalized pneumonia: a 10-year population-based study in Denmark. *J Intern Med* 2006; 259: 410–417.
24. Froes F, Diniz A, Mesquita M, *et al.* Hospital admissions of adults with community-acquired pneumonia in Portugal between 2000 and 2009. *Eur Respir J* 2013; 41: 1141–1146.
25. Christensen K, Doblhammer G, Rau R, *et al.* Aging populations: the challenges ahead. *Lancet* 2009; 374: 1196–1208.
26. Almirall J, Bolíbar I, Serra-Prat M, *et al.* New evidence of risk factors for community-acquired pneumonia: a population-based study. *Eur Respir J* 2008; 31: 1274–1284.
27. Durando P, Faust SN, Fletcher M, *et al.* Experience with pneumococcal polysaccharide conjugate vaccine (conjugated to CRM197 carrier protein) in children and adults. *Clin Microbiol Infect*, 2013: Suppl. 1, 1–9.
28. Taylor JK, Fleming GB, Singanayagam A, *et al.* Risk factors for aspiration in community-acquired pneumonia: analysis of a hospitalized UK cohort. *Am J Med* 2013; 126: 995–1001.
29. Cabre M, Serra-Prat M, Palomera E, *et al.* Prevalence and prognostic implications of dysphagia in elderly patients with pneumonia. *Age Ageing* 2010; 39: 39–45.
30. Calverley PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
31. Calverley PMA. Inhaled corticosteroids as a cause of CAP. *In*: Chalmers JD, Pletz MW, Aliberti S, eds. Community-Acquired Pneumonia. *Eur Respir Monogr* 2014; 63: 234–242.
32. Eom CS, Jeon CY, Lim JW, *et al.* Use of acid-suppressive drugs and risk of pneumonia: a systemic review and meta-analysis. *CMAJ* 2011; 183: 310–309.
33. Fillon KB, Chateau D, Targownik LE, *et al.* Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis. *Gut* 2013 [In press DOI: 10.1136/gutjnl-2013-304738].
34. Blasi F, Mantero M, Santus P, *et al.* Understanding the burden of pneumococcal disease in adults. *Clinical Microbiology and Infection* 2012; 18: 7–14.

35. Chalmers JD, Mandal P, Singanayagam A, *et al.* Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. *Intensive Care Med* 2011; 37: 1409–1420.
36. Wunsch H, Angus DC, Harrison DA, *et al.* Comparison of medical admissions to intensive care units in the United States and United Kingdom. *Am J Respir Crit Care Med* 2011; 183: 1666–1673.
37. Bauer TT, Welte T, Strauss R, *et al.* Why do nonsurvivors from community-acquired pneumonia not receive ventilator support? *Lung* 2013; 191: 417–424.
38. Froes F. Pneumonia da comunidade no adulto em Portugal Continental – incidencia emortalidade dos internamentos hospitalares nos anos de 1998 a 2000 [Pneumonia in the adult population in continental Portugal – incidence and mortality in hospitalized patients from 1998 to 2000]. *Rev Port Pneumol* 2003; 9: 187–194.
39. Sintes H, Sibila O, Waterer GW, *et al.* Severity assessment tools in CAP. *In*: Chalmers JD, Pletz MW, Aliberti S, eds. Community-Acquired Pneumonia. *Eur Respir Monogr* 2014; 63: 88–104.
40. Lung M, Rello J. Microbiology of bacterial CAP using traditional and molecular techniques. *In*: Chalmers JD, Pletz MW, Aliberti S, eds. Community-Acquired Pneumonia. *Eur Respir Monogr* 2014; 63: 25–41.
41. Koivula I, Stén M, Mäkelä PH. Prognosis after community-acquired pneumonia in the elderly: a population-based 12-year follow-up study. *Arch Intern Med* 1999; 159: 1550–1555.
42. Capelastegui A, España Yandiola PP, Quintana JM, *et al.* Predictors of short-term rehospitalisation following discharge of patients hospitalised with community-acquired pneumonia. *Chest* 2009; 136: 1079–1085.
43. Johnstone J, Eurich D, Majumdar S, *et al.* Long-term morbidity and mortality after hospitalization with community-acquired pneumonia: a population-based cohort study. *Medicine* 2008; 87: 329–334.
44. Yende S, Angus D, Ali IS, *et al.* Influence of comorbid conditions on long-term mortality after pneumonia in older people. *J Am Geriatr Soc* 2007; 55: 518–525.
45. Singanayagam A, Elder DH, Chalmers JD. Is community-acquired pneumonia an independent risk factor for cardiovascular disease? *Eur Respir J* 2012; 39: 187–196.
46. el Moussaoui R, Opmeer BC, de Borgie CAJM, *et al.* Long-term symptom recovery and health-related quality of life in patients with mild-to-moderate-severe community-acquired pneumonia. *Chest* 2006; 130: 1165–1172.
47. Monge V, San-Martin VM, Gonzalez A. The burden of community-acquired pneumonia in Spain. *Eur J Public Health* 2001; 11: 362–364.
48. Dal Negro R, Berto P, Tognella S, *et al.* Cost-of-illness of lung disease in the TriVeneto Region, Italy: the GOLD Study. *Monaldi Arch Chest Dis* 2002; 57: 3–9.
49. Bartolomé M, Almirall J, Morera J, *et al.* A population-based study of the costs of care for community-acquired pneumonia. *Eur Respir J* 2004; 23: 610–616.
50. Bauer TT, Welte T, Ernen C, *et al.* Cost analyses of community-acquired pneumonia from the hospital perspective. *Chest* 2005; 128: 2238–2246.
51. Tomasz A. Antibiotic resistance in *Streptococcus pneumoniae*. *Clin Infect Dis* 1997; 24: Suppl. 1, S85–S88.
52. Aspa J, Rajas O, Rodríguez de Castro F, *et al.* Drug-resistant pneumococcal pneumonia: clinical relevance and related factors. *Clin Infect Dis* 2004; 38: 787–798.
53. Pallares R, Liñares J, Vadillo M, *et al.* Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. *NEJM* 1995; 333: 474–480.
54. Song JH, Jung SI, Ki HK, *et al.* Clinical outcomes of pneumococcal pneumonia caused by antibiotic resistant strains in Asian countries: a study of the Asian Network for Surveillance of Resistant Pathogens. *Clin Infect Dis* 2004; 38: 1570–1578.
55. Friedland IR. Comparison of the response to antimicrobial therapy of penicillin-resistant and penicillin-susceptible pneumococcal disease. *Paediatr Infect Dis J* 1995; 14: 885–890.
56. Mascimento-Carvalho C, Cardoso MR, Brandileone MC, *et al.* Penicillin/ampicillin efficacy among children with severe pneumonia due to penicillin-resistant pneumococcus (MIC=4 μg mL^{-1}). *J Med Microbiol* 2009; 58: 1390–1392.
57. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 4.0, 2014. www.eucast.org/
58. Daneman N, McGeer A, Green K, *et al.* Macrolide resistance in bacteraemic pneumococcal disease: implications for patient management. *Clin Infect Dis* 2006; 43: 432–438.
59. Fuller JD, Low DE. A review of *Streptococcus pneumoniae* infection treatment failures associated with fluoroquinolone resistance. *Clin Infect Dis* 2005; 41: 118–121.
60. European Centre for Disease Prevention and Control. Antimicrobial Resistance Surveillance in Europe 2012. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm, ECDC, 2013; pp. 51–58.
61. Clinical and Laboratory. Standards Institute. M100-S24 Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fourth Informational Supplement. Wayne, Clinical Laboratory Standards Institute, 2014.
62. Lonks JR, Garau J, Gomez L, *et al.* Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant *Streptococcus pneumoniae*. *Clin Infect Dis* 2002; 35: 556–564.
63. Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Emerg Infect Dis* 2004; 10: 514–517.
64. Bronzwaer SL, Cars O, Buchholz U, *et al.* A European study on the relationship between antimicrobial use and antimicrobial resistance. *Emerg Infect Dis* 2002; 8: 278–282.

65. Guillemot D, Carbon C, Balkau B, *et al.* Low dosage and long treatment duration of β-lactam: risk factors for carriage of penicillin-resistant *Streptococcus pneumoniae. JAMA* 1998; 279: 365–370.
66. Gonzales R, Malone DC, Maselli JH, *et al.* Excessive antibiotic use for acute respiratory infections in the United States. *Clin Infect Dis* 2001; 33: 757–762.
67. Soares S, Kristinsson KG, Musser JM, *et al.* Evidence for the introduction of a multiresistant clone of serotype 6B *Streptococcus pneumoniae* from Spain to Iceland in the late 1980s. *J Infect Dis* 1993; 168: 158–163.
68. Munoz R, Coffey TJ, Daniels M, *et al.* Intercontinental spread of a multiresistant clone of serotype 23F *Streptococcus pneumoniae. J Infect Dis* 1991; 164: 302–306.
69. Liñares J, Ardanuy C, Pallares R, *et al.* Changes in antimicrobial resistance, serotypes and genotypes in *Streptococcus pneumoniae* over a 30-year period. *Clin Microbiol Infect* 2010; 16: 402–410.
70. Moberley S, Holden J, Tatham DP, *et al.* Vaccines for preventing pneumococcal infection in adults. *Cochrane Database Syst Rev* 2013; 1: CD000422.
71. Immunisation against respiratory diseases. *In*: Gibson GJ, Loddenkemper R, Sibille Y, *et al*, eds. The European Lung White Book. Respiratory Health and Disease in Europe. Sheffield, European Respiratory Society, 2013. pp. 306–315.
72. Moore MR, Hyde TB, Hennessy TW, *et al.* Impact of a conjugate vaccine on community-wide carriage of nonsusceptible *Streptococcus pneumonia* in Alaska. *J Infect Dis* 2004; 190: 2031–2038.
73. Pletz MW, Welte T. Pneumococcal and influenza vaccination. *In*: Chalmers JD, Pletz MW, Aliberti S, eds. Community-Acquired Pneumonia. *Eur Respir Monogr* 2014; 63: 266–284.
74. Ewig S, Welte T, Chastre J, *et al.* Rethinking the concepts of community-acquired and health-care-associated pneumonia. *Lancet Infect Dis* 2010; 10: 279–287.
75. Ewig S, Welte T, Torres A. Is healthcare-associated pneumonia distinct entity needing specific therapy? *Curr Opin Infect Dis* 2012; 25: 166–175.
76. Chalmers JD, Taylor JK, Singanayagam A, *et al.* Epidemiology, antibiotic therapy and clinical outcomes in healthcare associated pneumonia: a UK cohort study. *Clin Infect Dis* 2011; 53: 107–113.
77. Kollef MH, Shorr A, Tabak YP, *et al.* Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest* 2005; 128: 3854–3862.
78. Chalmers JD, Rother C, Salih W, *et al.* Healthcare-associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. *Clin Infect Dis* 2014; 58: 330–339.
79. Ewig S. The pneumonia triad. *In*: Chalmers JD, Pletz MW, Aliberti S, eds. Community-Acquired Pneumonia. *Eur Respir Monogr* 2014; 63: 13–24.
80. Aliberti S, Cillonez C, Chalmers JD, *et al.* Multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia: a European perspective. *Thorax* 2013; 68: 997–999.
81. Carratalà J, Mykietiuk A, Fernández-Sabé N, *et al.* Health care-associated pneumonia requiring hospital admission: epidemiology, antibiotic therapy, and clinical outcomes. *Arch Intern Med* 2007; 167: 1393–1399.
82. Carrabba M, Zarantonello M, Bonara P, *et al.* Severity assessment of heathcare-associated pneumonia and pneumonia in immunosuppression. *Eur Respir J* 2012; 40: 1201–1210.

Chapter 2

The pneumonia triad

Santiago Ewig

SUMMARY: The pneumonia triad includes community-acquired pneumonia (CAP), nosocomial pneumonia and pneumonia in the immunosuppressed host. The triad allows for clinical decisions regarding initial assessment of severity, selection of treatment setting, extent of diagnostic testing and empiric antimicrobial treatment.

CAP in elderly patients and those in nursing homes, albeit with different clinical characteristics, could not be proven to be associated with different pathogen patterns to CAP. Recently, the concept of CAP has been challenged by healthcare-associated pneumonia (HCAP), including a set of predictors for the presence of multidrug-resistant (MDR) pathogens. However, HCAP criteria were poorly predictive for MDR pathogens. Attempts at defining individual predictors for such pathogens are ongoing. Hospitalisation and exposure to antimicrobial treatment within the last 3–6 months seem to be the most important predictive factors.

Nosocomial pneumonia occurs in non-ventilated and ventilated patients. Early and late onset pneumonia should be determined, with careful reference to the correct starting point (hospitalisation not intubation), as well as comorbidity and antimicrobial exposure. Several risk factors have been defined for the presence of MDR pathogens.

Pneumonia in the immunosuppressed host includes a variety of different immunosuppressive conditions which are associated with specific timetables and thresholds for different pathogen patterns.

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Up to a century ago, pneumonia was considered a single entity that was thought to be invariably caused by pneumococci [1]. In fact, to date, *Streptococcus pneumoniae* has remained the leading pathogen of pneumonia in hosts who acquire pneumonia in the community. The first differentiation from pneumococci was established with the beginning of the catastrophic influenza epidemic by the end of World War I. Initially misdiagnosed as a bacterium by R. Pfeiffer, influenza was identified by R. Shope as being caused by the first viral agent causing pneumonia, whereas *Haemophilus influenzae* was identified as another bacterium that may cause bacterial super infection. The next milestone was the identification of *Mycoplasma pneumoniae* as the first "atypical (bacterial) pathogen" in 1938 by REIMANN [2]. It took several decades to recognise two additional important "atypical" bacterial pathogens, namely *Legionella* spp. in 1977 [3] and *Chlamydia pneumoniae* (now *Chlamydophila pneumoniae*) in 1986 [4]. Other pathogens including

Staphylococcus aureus and *Enterobacteriaceae* were only exceptionally found. Such was the pathogen pattern behind pneumonia occurring in hosts in the community, until recently, it was undisputed that this type of pneumonia be referred to as community-acquired pneumonia (CAP).

In the meantime, along with increasing life expectancy and comorbidity, two different types of pneumonia emerged, *i.e.* nosocomial pneumonia and pneumonia in the immunosuppressed host. Whereas both have common pathogen patterns that are fundamentally different from CAP, the first is defined by the setting of pneumonia acquisition (in an immunocompetent host), the latter by a host with severe immunosuppression (regardless of the setting of pneumonia acquisition).

Definitions of the pneumonia triad

Together these three entities form the pneumonia triad. The classical form of the triad is summarised in table 1. Nosocomial acquisition is usually suspected in patients developing pneumonia after at least 48 h of hospitalisation. Severe immunosuppression refers to two specific predispositions: 1) a degree of immunosuppression that is associated with a risk of developing so-called opportunistic infections (*e.g. Pneumocystis jirovecii*, cytomegalovirus and aspergillosis, among many others); and 2) a type of immunosuppression that predisposes to specific pathogen patterns. Neither opportunistic infections nor any comparable specific pathogen patterns are observed in CAP and nosocomial pneumonia. In contrast, the definition does not refer to an increased risk of infection as, although these patients are clearly at high risk of infections, this would be difficult to separate from the increased risk present in many patients with other pneumonias (*e.g.* elderly, several comorbidities, *etc.*).

Addressing pneumonia as community acquired, nosocomial or pneumonia in the immunosuppressed host requires us to keep in mind the structure of the whole triad in which one definition is based on contrasting elements of the other two.

Challenges of the pneumonia triad

It goes without saying that such classification implies a considerable simplification. Nevertheless, for a long time this "triad" of pneumonia has been an accepted pragmatic framework for the classification of patients with pneumonia, as well as for management approaches. It is important to recognise that the pneumonia triad is not just an academic classification for textbooks but represents a concept to be applied in clinical practice, *e.g.* CAP, such that diagnosis implies a complete specific standard of procedures in terms of severity assessment, and selection of treatment setting, diagnostic tests and initial antimicrobial treatment. The same is true for the remaining two entities.

However, recently this triad has been seriously challenged. Several authors have claimed that this triad is no longer adequate in facing the challenge of recognising multidrug-resistant (MDR) pathogens [5–7]. As a consequence, healthcare-associated pneumonia (HCAP) was introduced as a new entity in the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) update on nosocomial pneumonia [8]. The modified pneumonia triad is shown in table 2.

Table 1. Classical pneumonia triad

	Setting of acquisition	Immune status
Community-acquired pneumonia	Community	Immunocompetent
Nosocomial pneumonia	Hospital	Immunocompetent
Pneumonia in the immunosuppressed host	Any	Severe immunosuppression[#]

[#]: patients are at increased risk of so-called opportunistic infections.

Table 2. Modified pneumonia triad

	Setting of acquisition	Immune status
Community-acquired pneumonia	Community, including NHAP and dialysis[#]	Immunocompetent
Nosocomial pneumonia	Hospital or having been hospitalised within the last 3–6 months and having received antimicrobial treatment	Immunocompetent
Pneumonia in the immunosuppressed host	Any	Severe immunosuppression[¶]

NHAP: nursing home-acquired pneumonia. [#]: patients with risk factors (severe pulmonary comorbidity, repeated hospitalisation, antimicrobial treatment, bedridden status, and known bronchopulmonary colonisation with multidrug-resistant pathogens) should be considered to be at risk of multidrug-resistant pathogens; [¶]: patients are at increased risk of so-called opportunistic infections.

This chapter is dedicated to the discussion of the challenges of the triad and provides a perspective for future refinements of the conceptual framework of pneumonia.

Challenges to the concept of CAP

Pneumonia in the elderly

Increasing life expectancy, at least in western countries, has inevitably increased the number of patients at older age who are prone to pneumonia. As a consequence, CAP is a condition that most frequently affects persons aged 60 years or over. Data from the national quality performance programme of hospitalised patients with CAP from Germany show that approximately 80% of CAP patients were aged greater than 60 years [9]. In fact, much work has been carried out to study the implications of older ages on the clinical characteristics of CAP, particularly the pathogen patterns. Several studies dedicated to pneumonia in the elderly [10–16] or pneumonia in the very elderly [17–19], defined as pneumonia acquired in the community in patients aged 65 years or over and 75 years or over, respectively, could prove that these patients experienced more severe pneumonia, more complications, had a longer length of stay and higher mortality compared to the younger patients. However, differences in pathogen patterns were usually limited. Some studies found more aspiration, others a higher incidence of *Enterobacteriaceae* and MDR pathogens, but these differences were usually small.

CAP in the younger

Recently, we stated that CAP in the younger adults might be an entity of its own. In fact, many characteristics represent the opposite of those observed in the elderly, *e.g.* pneumonia that is more symptomatic, less severe, less complicated and less fatal. However, there was evidence that younger patients experience CAP due to *M. pneumoniae* much more frequently and, depending on the type of influenza virus, may also experience influenza-associated CAP much more frequently [20].

The difference between younger and older ages formed a continuum, with the mid-seventh decade being a notable threshold for the change of all characteristics. However, the clinical characteristics of elderly patients were shown to be even more pronounced in those residing in nursing homes, suggesting a heavy bearing of functional dependence on the clinical characteristics and outcome of CAP. Based on these data, it may be reasonable to subdivide CAP into three subentities: 1) CAP in the younger, 2) CAP in the elderly independent population, and 3) CAP in the elderly dependent population, with age 65 years being a well-evidenced threshold.

Community-acquired aspiration pneumonia is a difficult to define subgroup within the CAP aetiology. Aspiration may occur without pneumonia, resulting in chemical or infectious

pneumonia, or both. It is unclear to what extent silent aspiration should be addressed separately since it occurs very frequently in elderly patients. It seems prudent to restrict such diagnosis of aspiration pneumonia to patients with witnessed aspiration presenting with typical features of aspiration, *i.e.* infiltrates in dependent lung segments, with or without abscess formation.

Nursing home-acquired pneumonia

GARB *et al.* [21] were the first to describe the entity of nursing home-acquired pneumonia (NHAP) in 1978. In that study, patients with NHAP had not only poorer outcomes but also significantly more frequent *S. aureus* and *Klebsiella pneumoniae* [21]. At that time, NHAP was then a widely accepted entity in the USA and Canada, requiring broad-spectrum antimicrobial treatment with activity against methicillin-resistant *S. aureus* (MRSA) and Gram-negative pathogens, including nonfermenters.

In several studies, this difference could not be consistently reproduced. Whereas US and Canadian authors at least found differences large enough to support the NHAP entity [22–25], none of the European studies published to date have demonstrated such differences [26–28]. In Germany, in the largest study conducted to date, elderly patients residing at home and elderly patients residing at nursing homes were compared. Large differences in outcomes were found but only marginal differences were found in aetiology [28]. Overall, the NHAP concept has not gained widespread acceptance in Europe, as is the case in the USA and Canada.

Healthcare-associated pneumonia

The concept of HCAP was introduced in 2005 in the updated ATS/IDSA guidelines for the management of nosocomial pneumonia (and HCAP) [8]. Based on single centre data published in the same year, the authors claimed that patients with HCAP criteria have a high mortality similar to that of nosocomial pneumonia. This increased mortality was a consequence of unexpected pathogens not covered by initial antimicrobial treatment that followed the concept of CAP, thus directly linking exceptional pathogen patterns to excess mortality. Those unexpected potentially MDR pathogens were thought to arise from contacts in healthcare institutions such as hospitals, nursing homes, dialysis, ambulatory services, *etc.* Consequently, the authors recommended broad antimicrobial treatment for patients meeting HCAP criteria following the treatment administered to high-risk patients with nosocomial pneumonia.

This concept has been subject to extensive and very detailed criticism [29–31]. The fact that patients meeting HCAP criteria might have an excess of MDR pathogens and the postulated link between MDR pathogens and excess mortality was challenged. Three European studies including complete and comprehensive prospective microbiological investigations, two from Spain [32, 33] and one from the UK [34], failed to substantiate the HCAP concept. Most recently, a meta-analysis of all studies dealing with HCAP to date could not verify the main hypotheses of HCAP. In fact, even the excess mortality was shown to be associated with increased comorbidity and to disappear if adjusted for that confounder [35]. Overall, HCAP was not found to be a valid predictor of the presence of MDR pathogens. Another meta-analysis of guideline-concordant treatment of patients with HCAP failed to demonstrate an advantage for those receiving guideline-concordant treatment [36]. Thus, applying HCAP would favour excess overtreatment and thereby seriously increase selection pressure and multidrug-resistance.

Two predictive rules for MDR pathogens have been established and validated [37–40]. Both share several variables and a similar weighting of these variables (table 3). The predictions of the presence of MDR pathogens were superior to HCAP in the individual patient. However, derivation and validation studies of both rules, particularly the study by SHORR *et al.* [38], had a high prevalence of MDR pathogens (thereby a high pretest probability), not reproduced by any working group. As a result, both would work considerably worse in settings with low prevalence of MDR pathogens and continue to be associated with considerable overtreatment if applied in clinical practice.

Table 3. Predictive rules for the presence of multidrug-resistant pathogens in patients meeting healthcare-associated pneumonia criteria

	Points
Rule 1 [37, 38]	
Recent hospitalisation	4
Nursing home residency	3
Chronic haemodialysis	2
Critically ill	1
Rule 2 [39, 40]	
Hospitalisation for ⩾2 days in the preceding 90 days	4
Nursing home residency or extended care facility	3
Chronic renal failure	5
Comorbidity, *i.e.* at least one of the following: cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, antimicrobial therapy in preceding 90 days, immunosuppression, home wound care, home infusion therapy (including antibiotics)	0.5

SHINDO *et al.* [41] present the third set of predictors of pathogens resistant to standard treatment in patients meeting CAP and HCAP criteria. These include prior hospitalisation, immunosuppression, previous antibiotic use, use of gastric acid suppressive agents, tube feeding and non-ambulatory status. The authors show that an increased number of risk factors increases the risk of MDR pathogens. A detailed criticism of this study was recently provided, mainly focusing on the methodological issues raised previously [29–31, 42].

A Japanese study validated an algorithm proposed by BRITO and NIEDERMAN [43], keeping HCAP as an indicator of a possible risk for MDR but further stratifying such risk into four groups with four main risk factors: previous hospitalisation, recent antibiotics, poor functional status and immune suppression. MDR pathogens were more common in HCAP *versus* CAP (15.3% *versus* 0.8%; $p<0.001$). 93.1% of HCAP patients were treated according to this algorithm, with only 53% receiving broad-spectrum empiric therapy, yet 92.9% received appropriate therapy for the identified pathogen [44]. However, this rule is very complicated and includes duplicate stratifications (*e.g.* previous hospitalisation is part of the definition of HCAP and repeatedly listed as a risk factor in further stratification), and could be reduced to a list of risk factors resembling that of SHORR and co-workers [37, 38] and ALIBERTI and co-workers [39, 40] (table 3).

Critical appraisal

Overall, the concept to link increasing age with an increase in difficult-to-treat and potential MDR pathogens has proved to be a misperception. In fact, age as such does not confer different risks for pathogens. On the contrary, it is the risk for *S. pneumoniae* that steadily increases with age [28]. Likewise, residency at a nursing home has not been shown to be a valid predictor for MDR pathogens. This is not surprising since the definitions of a nursing home facility have not been standardised, and such facilities may vary considerably in the range of independency of residents and standards of care. The differences in rates of MDR pathogens identified in the USA and Europe may be explained by the differing prevalence of such pathogens, *e.g.* the prevalence of MRSA in nursing home residents in Germany was 2%, which appears to be a very low compared to US data [28]. Other healthcare facilities, such as dialysis and home wound services, also seemingly do not confer a specific risk factor for MDR pathogens. Recently, a large Spanish study failed to identify pathogens uncommon for CAP in the population on long-term dialysis [33].

However, dependency as well as comorbidity, in particular pulmonary comorbidity such as severe chronic obstructive pulmonary disease and/or bronchiectasis and known bronchopulmonary colonisation with MDR, has been found to be associated with MDR pathogens [45, 46]. Again, this might not be due to dependency and comorbidity as such, but may be due to the frequency of antimicrobial treatment cycles and hospitalisations in the past. It appears that dependency and severe comorbidity may simply reflect this history of repeated exposure to antimicrobial treatment in the hospital setting.

This is the reason why patients with recent hospitalisation and antimicrobial treatment may be regarded as being at increased risk for MDR pathogens. It has not been possible to identify a precise threshold for the time prior to the development of pneumonia qualifying for such risk, but 3–6 months is a reasonable timeframe. Thus, patients presenting with pneumonia acquired in the community but who have been hospitalised and treated with antimicrobial treatment in the last 3–6 months may qualify as nosocomial pneumonia and receive treatment according to the standards of care of that entity [39–42, 44–46]. However, it appears increasingly mandatory to recognise that many patients with advanced age and comorbidity are candidates for limitations of treatment due to considerations of futility. Such considerations should be incorporated in treatment algorithms of CAP in order to avoid overtreatment in these patients.

Age and functional status (in patients not recently hospitalised and not having received antimicrobial regimens) may be reasonable variables to subdivide CAP into three entities (table 4). The advantages of such age-based subdivision are not only relevant for the selection of initial antimicrobial treatment but for the understanding of different clinical presentations, expectance of complications and estimation of prognosis.

Clinicians may feel some discomfort classifying patients with pneumonia associated diabetes mellitus, liver cirrhosis or chronic kidney failure as CAP and thereby as ''immunocompetent'', and they may feel safer when extending initial empiric antimicrobial treatment to a broad-spectrum regimen, as indicated in patients with severe immunosuppression. As a matter of fact, there is no evidence that such patients may be in need of a broader treatment. All three populations have only recently been extensively studied [47–49], and no study found any pathogen patterns resembling those of patients with severe immunosuppression.

In conclusion, CAP is still proven to be a valid entity, both in terms of systematic classification as well as in terms of a clinical concept. However, the need for the identification of individual patients at risk of MDR pathogens is an important modification. Age-based subdivisions may be of additional clinical value. Otherwise, several comorbidities albeit clearly associated with some degree of immunosuppression, do not confer a risk for MDR pathogens. Therefore, patients with such comorbidities can still be included.

Nosocomial pneumonia

Implications of nosocomial pneumonia

Most available data on nosocomial pneumonia relate to patients being mechanically ventilated. Only comparably few data are available for nosocomial pneumonia in the non-intubated patient, and the same is true for those on tracheostomy. However, available data to date do not indicate that differences in these groups are extensive, so it seems reasonable to rely on the data we have when classifying nosocomial pneumonia.

Table 4. Subentities of community-acquired pneumonia (CAP)

	CAP in the younger[#]	CAP in the independent elderly[¶]	CAP in the dependent elderly[¶]
Clinical symptoms	Higher symptom score	Lower symptom score	Lower symptom score
Initial severity	Less severe	More severe	More severe
Complications	Less frequent	More frequent	More frequent
MDR pathogens	Virtually absent	Rare	More frequent
Treatment limitation	Rare[+]	Rare, more frequent at higher ages	Frequent
Mortality	Very low (<5%)	Increased (<10%)	High (20–40%)

MDR: multidrug-resistant. [#]: age <64 years; [¶]: age ⩾65 years; [+]: younger dependent patients still share the main patterns of clinical presentation of this age group and have lower mortality.

Nosocomial pneumonia in the mechanically ventilated patient is usually termed as ventilator-associated pneumonia (VAP); this is clearly a misnomer since the ventilator has nothing to do with the pathogenesis of such pneumonia. Instead, the correct term (in order to avoid changing the generally accepted abbreviation VAP) would be (invasive) ventilation-associated pneumonia [50].

Pathogen patterns in patients with nosocomial pneumonia generally differ from those with CAP, exerting a higher rate of *Staphylococcus*, enterobacteria and nonfermenters, thus resulting in high rates of MDR pathogens. The exact relative frequencies vary considerably across different hospitals, depending on: 1) local treatment setting; 2) standards of hygiene; 3) policy of antimicrobial treatment; and 4) cooperation with other hospitals and facilities (rate of imported pathogens). The problem of MDR pathogens in intensive care units is thought to be dependent on a high selection pressure due to extensive antimicrobial treatment, resulting in induction of resistance of the infecting pathogen. As well as a high local prevalence of MDR pathogens that may readily be directly transferred to patients, mainly by contaminated hands of hospital staff.

Early and late nosocomial pneumonia

There is clear evidence that in severely compromised patients colonisation of the upper respiratory tract with typical nosocomial pathogens takes places within 48 h. This is the rationale behind the concept of early and late nosocomial pneumonia. This concept implies that patients with early pneumonia mainly exert pathogens of standard local flora (*i.e. Staphylococcus*, *Streptococcus* and *H. influenzae*) descending to the lower respiratory tract during intubation [51–54]. Those with late pneumonia are additionally subject to infection with the nosocomial, difficult-to-treat and potentially multi-resistant colonisers (MRSA, extended-spectrum β-lactamase-producing *Enterobacteriaceae* and nonfermenters) resulting from permanent dissemination of these pathogens along the respiratory tube. Thus, early pneumonia may be termed intubation-associated pneumonia, whereas late pneumonia may be regarded as respiratory tube-associated pneumonia.

This concept has been challenged by several studies aiming to demonstrate that this classification does not consistently differentiate such pathogen patterns [55–57]. However, these studies have mistaken the concept by missing the fact that the adequate starting point for classifying pneumonia as early or late is the day of hospitalisation (not the day of intubation). Moreover, they ignored that the normal flora requires pre-morbidly healthy patients and that it is very vulnerable to any antimicrobial exposure [52, 54, 56]. As a consequence, patients with early pneumonia and risk factors (pretreatment and comorbidities) were classified as patients at risk for the pathogen pattern of late pneumonia in the original ATS/IDSA guidelines. Intubation, as such, may take place at any point of hospitalisation; however, colonisation will take place in the first 48 h. Accordingly, intubation is only the adequate starting point for classifying nosocomial pneumonia if it occurs before or immediately after hospitalisation (fig. 1). Even so, it is noteworthy that the trends of pathogen frequencies still followed the concept of early and late pneumonia in a recent study [57].

It has seldom been appreciated that, to some extent, the concept of early and late nosocomial pneumonia challenges the traditional definition of nosocomial pneumonia as a pneumonia occurring at least 48 h after hospitalisation. In practical terms, this is less worrisome since patients with (correctly defined) early onset pneumonia will receive a similar treatment (broad-spectrum β-lactam) compared to those with CAP. The issue of covering atypical pathogens in patients developing nosocomial pneumonia within the first 48 h of hospitalisation has not been addressed.

Nosocomial pneumonia without and with risk factors for MDR pathogens

Clearly, early and late pneumonia may be adequately captured if recognised as one risk factor among others. For this reason, this concept has not been conserved by the latest update of the ATS/IDSA guidelines as the main guide on empiric initial antimicrobial treatment [8]. Currently, it is more adequate to address nosocomial pneumonia as one without or with risk factors. The list of potential risk factors is listed in table 5.

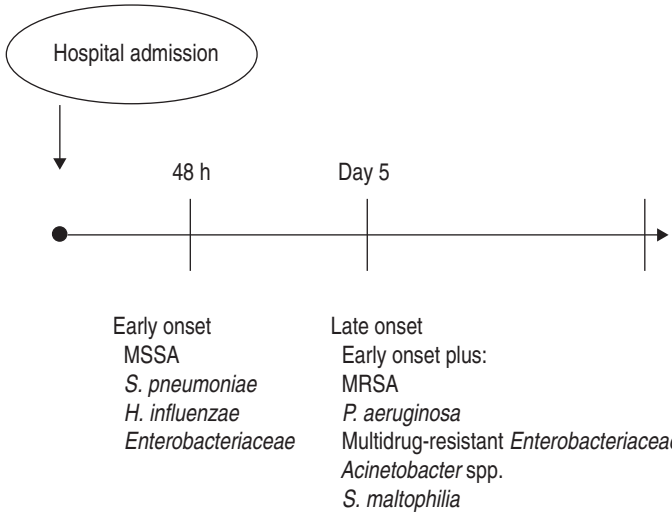

Figure 1. Timetable of early *versus* late onset nosocomial pneumonia. The 48-h threshold to differentiate nosocomial pneumonia from community-acquired pneumonia does not apply in this concept. In the presence of comorbidity affecting tracheobronchial colonisation and antimicrobial pretreatment, risk profile shifts to late onset pneumonia by definition. MSSA: methicillin-susceptible *Staphylococcus aureus*; *S. pneumoniae*: *Streptococcus pneumoniae*; *H. influenzae*: *Haemophilus influenzae*; MRSA: methicillin-resistant *S. aureus*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *S. maltophilia*: *Stenotrophomonas maltophilia*.

Nosocomial pneumonia in immunosuppressed patients

Not all studies on nosocomial pneumonia have consistently excluded severe immunosuppression. However, studies particularly focusing on nosocomial pneumonia in severely immunosuppressed hosts are difficult to conduct due to the fact that it may be problematic to judge an infection which has developed in the hospital as nosocomial. An illustrative example might be the development of *P. jirovecii* pneumonia; although it has been established that such pneumonia may be transferred nosocomially, other pneumonias may have reactivated. Therefore, it seems adequate to classify them all as pneumonia in the immunosuppressed host, regardless of the setting of acquisition.

Pneumonia in the immunosuppressed host

This entity can most accurately be subdivided according to the type of immunosuppression. The main divisions relate to inborn and acquired immunosuppression, further to the main types of predominant immune deficiency; T-cell, B-cell or neutropenic (table 6). Further differentiations may be made according to specific immunosuppressive drugs.

The list of conditions of immunosuppression is continuously growing due to progression in drug development and definition of rare immunosuppressive conditions. In general, the four types of immunosuppression in table 6 are associated with characteristic programmes and thresholds defining risk factors for specific opportunistic pathogens [58].

The programme after solid organ and stem cell transplantation includes an early and late phase, with neutropenia-associated bacterial infections being typically prevalent in the early phase (up to 4 weeks after engraftment) and T-cell depletion-associated classical opportunistic pathogens in the late phase (5–180 days after engraftment). Following this, the risk depends on the intensity of immunosuppression needed to prevent graft rejection [59–61].

Expected pathogen patterns in HIV-associated immunosuppression can readily be predicted following CD4 cell counts. Whereas bacterial pneumonia pathogen patterns established for patients with CAP can be expected in HIV-infected patients with CD4 cell counts up to greater than 500 cells·μL^{-1}, the risk for tuberculosis increases at early stages of CD4 cell depletion (less than 500 cells·μL^{-1}). CD4 cell counts less than 200 cells·μL^{-1} confer a high risk for *P. jirovecii*. Cytomegalovirus infection usually requires

Table 5. Risk factors for the presence of multidrug-resistant (MDR) pathogens in nosocomial pneumonia

Structural lung disease
Known colonisation with MDR pathogens
Antimicrobial treatment
Hospitalisation (>4 days, late onset pneumonia)
Treatment at the intensive care unit
Prolonged invasive ventilation (>4–7 days)
Malnutrition

Table 6. Examples of types of pneumonia in the severely immunosuppressed host

Type of pneumonia	Example
Pneumonia in patients with predominant T-cell depletion	HIV infection and AIDS Late-phase solid organ and stem cell transplantation
Pneumonia in patients with predominant B-cell depletion	Acquired humoral immune deficiencies
Pneumonia in patients with neutropenia	During antineoplastic chemotherapy Early-phase solid organ and stem cell transplantation
Pneumonia in patients receiving immunosuppressive medications	Steroids Azathioprine, methotrexate, cyclosporin A, calcineurin inhibitors (sirolimus and tacrolimus) Fludarabine Anti-CD-20 (rituximab) Anti-CD-52 (alemtuzumab) TNF-α inhibitors (infliximab, adalimumab and etanercept)

The table primarily addresses acquired immune deficiencies. Inborn cellular and humoral or combined immunodeficiency are also classified as being primarily cellular, humoral or combined. Steroids are the most common reason for iatrogenic immunosuppression; however, there is a long list of other drugs that are involved. TNF: tumour necrosis factor.

much lower CD4 cell counts (less than 50 cells·μL^{-1}), and fungal infections such as Aspergillosis are usually observed in generalised immunodepletion, including neutropenia [62, 63].

The pathogen patterns observed in neutropenia depend on the extent and duration of neutropenia. Severe neutropenia (neutrophil count less than 500 cells·μL^{-1}) confers a high risk for bacterial pathogens, and the risk for fungal infections, particularly invasive Aspergillosis, increases with the duration of neutropenia (greater than 10 days) [64].

Finally, iatrogenic immunosuppression with steroids increases the risk of bacterial pneumonia (at very low dosages for over 2 weeks) [65] and, depending on dosage and duration of the steroid medication, fungal infections (primarily *P. jirovecii* and invasive Aspergillosis) [66, 67]. Depending on the mechanism of immunosuppression, every immunosuppressive drug is associated with its particular pathogen pattern. For example, tumour necrosis factor-α inhibitors predispose to tuberculosis reactivation due to inhibition of the key mechanism of control for the *Mycobacterium tuberculosis* complex [68].

In general, no relevant modification has proved to be necessary in the definition of this pneumonia group in the immunosuppressed host, whereas the spectrum of particularly iatrogenic immunosuppression has largely increased with the introduction of new drugs, particularly antibodies.

Conclusions

The pneumonia triad is a useful framework for clinicians at the bedside to guide clinical management of patients with pneumonia. It directs the assessment of severity, treatment setting, type and extent of investigations required, and the initial antimicrobial treatment required.

Within the triad, the concept of CAP has been challenged by the concept of NHAP and HCAP. However, at least in European studies, the incidence of MDR pathogens not covered by current treatment recommendations is considerably low, and attempts to define individual risk factors, albeit with better predictions compared to HCAP, run a high risk of overtreatment. Thus, CAP is still a valid clinical concept. Today, patients with advanced structural lung disease and those known to be colonised with MDR pathogens are the most likely to have an MDR aetiology.

Obviously, patients who have been hospitalised in the last 3–6 months and who have been subject to antimicrobial treatment have a considerable risk for MDR pathogens and should be treated

according to the guidelines for nosocomial pneumonia. The majority of nosocomial pneumonia is ventilation associated.

An immunosuppressive state substantially impacts on how to approach a patient with pneumonia, and every effort must be made to assess the presence and type of immunosuppression. This is particularly true for conditions requiring immunosuppressive medications.

Statement of Interest

None declared.

References

1. Osler W. Principles and Practice in Medicine. New York, D. Appleton and Co., 1982.
2. Reimann HA. An acute infection of the respiratory tract with atypical pneumonia. A disease entity probably caused by a filtrable virus. *JAMA* 1984; 251: 936–944.
3. Fraser DW, Tsai TR, Orenstein W, *et al.* Legionnaires' disease: description of an epidemic of pneumonia. *N Engl J Med* 1977; 297: 1189–1197.
4. Grayston JT, Kuo CC, Wang SP, *et al.* A new *Chlamydia psittaci* strain, TWAR, isolated in acute respiratory tract infections. *N Engl J Med* 1986; 315: 161–168.
5. Kollef MH, Shorr A, Tabak YP, *et al.* Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest* 2005; 128: 3854–3862.
6. Micek ST, Kollef KE, Reichley RM, *et al.* Health care-associated pneumonia and community-acquired pneumonia: a single-center experience. *Antimicrob Agents Chemother* 2007; 51: 3568–3573.
7. Venditti M, Falcone M, Corrao S, *et al.* Outcomes of patients hospitalized with community-acquired, health care-associated, and hospital-acquired pneumonia. *Ann Intern Med* 2009; 150: 19–26.
8. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171: 388–416.
9. Ewig S, Birkner N, Strauss R, *et al.* New perspectives on community-acquired pneumonia in 388 406 patients. Results from a nationwide mandatory performance measurement programme in healthcare quality. *Thorax* 2009; 64: 1062–1069.
10. Venkatesan P, Gladman J, Macfarlane JT, *et al.* A hospital study of community acquired pneumonia in the elderly. *Thorax* 1990; 45: 254–258.
11. Riquelme R, Torres A, El-Ebiary M, *et al.* Community-acquired pneumonia in the elderly: a multivariate analysis of risk and prognostic factors. *Am J Respir Crit Care Med* 1996; 154: 1450–1455.
12. Riquelme R, Torres A, El-Ebiary M, *et al.* Community-acquired pneumonia in the elderly. Clinical and nutritional aspects. *Am J Respir Crit Care Med* 1997; 156: 1908–1914.
13. Lieberman D, Lieberman D, Schlaeffer F, *et al.* Community-acquired pneumonia in old age: a prospective study of 91 patients admitted from home. *Age Ageing* 1997; 26: 69–75.
14. Marrie TJ. Community-acquired pneumonia in the elderly. *Clin Infect Dis* 2000; 31: 1066–1078.
15. Kaplan V, Angus DC, Griffin MF, *et al.* Hospitalized community-acquired pneumonia in the elderly: age- and sex-related patterns of care and outcome in the United States. *Am J Respir Crit Care Med* 2002; 165: 766–772.
16. Zalacain R, Torres A, Celis R, *et al.* Community-acquired pneumonia in the elderly: Spanish multicentre study. *Eur Respir J* 2003; 21: 294–302.
17. El-Solh AA, Sikka P, Ramadan F, *et al.* Etiology of severe pneumonia in the very elderly. *Am J Respir Crit Care Med* 2001; 163: 645–651.
18. Fernández-Sabé N, Carratalà J, Rosón B, *et al.* Community-acquired pneumonia in very elderly patients: causative organisms, clinical characteristics, and outcomes. *Medicine (Baltimore)* 2003; 82: 159–169.
19. Janssens JP, Krause KH. Pneumonia in the very old. *Lancet Infect Dis* 2004; 4: 112–124.
20. Klapdor B, Ewig S, Pletz MW, *et al.* Community-acquired pneumonia in younger patients is an entity on its own. *Eur Respir J* 2012; 39: 1156–1161.
21. Garb JL, Brown RB, Garb JR, *et al.* Differences in etiology of pneumonias in nursing home and community patients. *JAMA* 1978; 240: 2169–2172.
22. Marrie TJ, Durant H, Kwan C. Nursing home-acquired pneumonia. A case-control study. *J Am Geriatr Soc* 1986; 34: 697–702.
23. Marrie TJ, Blanchard W. A comparison of nursing home-acquired pneumonia patients with patients with community-acquired pneumonia and nursing home patients without pneumonia. *J Am Geriatr Soc* 1997; 45: 50–55.
24. El-Solh AA, Pietrantoni C, Bhat A, *et al.* Microbiology of severe aspiration pneumonia in institutionalized elderly. *Am J Respir Crit Care Med* 2003; 167: 1650–1654.
25. El Solh AA, Pietrantoni C, Bhat A, *et al.* Indicators of potentially drug-resistant bacteria in severe nursing home-acquired pneumonia. *Clin Infect Dis* 2004; 39: 474–480.

26. Lim WS, Macfarlane JT. A prospective comparison of nursing home acquired pneumonia with community acquired pneumonia. *Eur Respir J* 2001; 18: 362–368.
27. Polverino E, Dambrava P, Cillóniz C, *et al.* Nursing home-acquired pneumonia: a 10 year single-centre experience. *Thorax* 2010; 65: 354–359.
28. Ewig S, Klapdor B, Pletz MW, *et al.* Nursing-home-acquired pneumonia in Germany: an 8-year prospective multicentre study. *Thorax* 2012; 67: 132–138.
29. Ewig S, Welte T, Chastre J, *et al.* Rethinking the concepts of community-acquired and health-care-associated pneumonia. *Lancet Infect Dis* 2010; 10: 279–287.
30. Ewig S, Welte T, Torres A. Is healthcare-associated pneumonia a distinct entity needing specific therapy? *Curr Opin Infect Dis* 2012; 25: 166–175.
31. Ewig S, Welte T. Adding fuel to the flames? It is time to leave HCAP. *Respir Med* 2012; 106: 1309–1310.
32. Carratalà J, Mykietiuk A, Fernández-Sabé N, *et al.* Health care-associated pneumonia requiring hospital admission: epidemiology, antibiotic therapy, and clinical outcomes. *Arch Intern Med* 2007; 167: 1393–1399.
33. Garcia-Vidal C, Viasus D, Roset A, *et al.* Low incidence of multidrug-resistant organisms in patients with healthcare-associated pneumonia requiring hospitalization. *Clin Microbiol Infect* 2011; 17: 1659–1665.
34. Chalmers JD, Taylor JK, Singanayagam A, *et al.* Epidemiology, antibiotic therapy, and clinical outcomes in health care-associated pneumonia: a UK cohort study. *Clin Infect Dis* 2011; 53: 107–113.
35. Chalmers JD, Rother C, Salih W, *et al.* Healthcare associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. *Clin Infect Dis* 2013 [In press DOI: 10.1093/cid/cit734].
36. Troitino AX, Porhomayon J, El-Solh AA. Guideline-concordant antimicrobial therapy for healthcare-associated pneumonia: a systematic review and meta-analysis. *Lung* 2013; 191: 229–237.
37. Shorr AF, Zilberberg MD, Micek ST, *et al.* Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. *Arch Intern Med* 2008; 168: 2205–2210.
38. Shorr AF, Zilberberg MD, Reichley R, *et al.* Validation of a clinical score for assessing the risk of resistant pathogens in patients with pneumonia presenting to the emergency department. *Clin Infect Dis* 2012; 54: 193–198.
39. Aliberti S, Di Pasquale M, Zanaboni AM, *et al.* Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. *Clin Infect Dis* 2012; 54: 470–478.
40. Aliberti S, Cillóniz C, Chalmers JD, *et al.* Multidrug-resistant pathogens in hospitalised patients coming from the community with pneumonia: a European perspective. *Thorax* 2013; 68: 997–999.
41. Shindo Y, Ito R, Kobayashi D, *et al.* Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2013; 188: 985–995.
42. Ewig S. HCAP not busy being born is busy dying. *Am J Respir Crit Care Med* 2013; (in press).
43. Brito V, Niederman MS. Healthcare-associated pneumonia is a heterogeneous disease, and all patients do not need the same broad-spectrum antibiotic therapy as complex nosocomial pneumonia. *Curr Opin Infect Dis* 2009; 22: 316–325.
44. Maruyama T, Fujisawa T, Okuno M, *et al.* A new strategy for healthcare-associated pneumonia: a 2-year prospective multicenter cohort study using risk factors for multidrug-resistant pathogens to select initial empiric therapy. *Clin Infect Dis* 2013; 57: 1373–1383.
45. Arancibia F, Bauer TT, Ewig S, *et al.* Community-acquired pneumonia due to gram-negative bacteria and *Pseudomonas aeruginosa*: incidence, risk, and prognosis. *Arch Intern Med* 2002; 162: 1849–1858.
46. von Baum H, Welte T, Marre R, *et al.* Community-acquired pneumonia through *Enterobacteriaceae* and *Pseudomonas aeruginosa*: diagnosis, incidence and predictors. *Eur Respir J* 2010; 35: 598–605.
47. Viasus D, Garcia-Vidal C, Cruzado JM, *et al.* Epidemiology, clinical features and outcomes of pneumonia in patients with chronic kidney disease. *Nephrol Dial Transplant* 2011; 26: 2899–2906.
48. Di Yacovo S, Garcia-Vidal C, Viasus D, *et al.* Clinical features, etiology, and outcomes of community-acquired pneumonia in patients with diabetes mellitus. *Medicine (Baltimore)* 2013; 92: 42–50.
49. Viasus D, Garcia-Vidal C, Castellote J, *et al.* Community-acquired pneumonia in patients with liver cirrhosis: clinical features, outcomes, and usefulness of severity scores. *Medicine (Baltimore)* 2011; 90: 110–118.
50. Torres A, Ewig S, Lode H, *et al.* Defining, treating and preventing hospital acquired pneumonia: European perspective. *Intensive Care Med* 2009; 35: 9–29.
51. Langer M, Cigada M, Mandelli M, *et al.* Early onset pneumonia: a multicenter study in intensive care units. *Intensive Care Med* 1987; 13: 342–346.
52. Sirvent JM, Torres A, El-Ebiary M, *et al.* Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma. *Am J Respir Crit Care Med* 1997; 155: 1729–1734.
53. Ewig S, Torres A, El-Ebiary M, *et al.* Bacterial colonization patterns in mechanically ventilated patients with traumatic and medical head injury. Incidence, risk factors, and association with ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1999; 159: 188–198.
54. Sirvent JM, Torres A, Vidaur L, *et al.* Tracheal colonisation within 24 h of intubation in patients with head trauma: risk factor for developing early-onset ventilator-associated pneumonia. *Intensive Care Med* 2000; 26: 1369–1372.
55. Ibrahim EH, Ward S, Sherman G, *et al.* A comparative analysis of patients with early-onset *vs* late-onset nosocomial pneumonia in the ICU setting. *Chest* 2000; 117: 1434–1442.
56. Verhamme KM, De Coster W, De Roo L, *et al.* Pathogens in early-onset and late-onset intensive care unit-acquired pneumonia. *Infect Control Hosp Epidemiol* 2007; 28: 389–397.

57. Gastmeier P, Sohr D, Geffers C, *et al.* Early- and late-onset pneumonia: is this still a useful classification? *Antimicrob Agents Chemother* 2009; 53: 2714–2718.
58. Agusti C, Torres A, eds. Pulmonary Infection in the Immunocompromised Patient: Strategies for Management. New York, John Wiley & Sons, 2009.
59. Chakinala MM, Trulock EP. Pneumonia in the solid organ transplant patient. *Clin Chest Med* 2005; 26: 113–121.
60. Küpeli E, Eyüboğlu FÖ, Haberal M. Pulmonary infections in transplant recipients. *Curr Opin Pulm Med* 2012; 18: 202–212.
61. Godbole G, Gant V. Respiratory tract infections in the immunocompromised. *Curr Opin Pulm Med* 2013; 19: 244–250.
62. Benito N, Moreno A, Miro JM, *et al.* Pulmonary infections in HIV-infected patients: an update in the 21st century. *Eur Respir J* 2012; 39: 730–745.
63. Capocci S, Lipman M. Respiratory infections in HIV-infected adults: epidemiology, clinical features, diagnosis and treatment. *Curr Opin Pulm Med* 2013; 19: 238–243.
64. Maschmeyer G, Beinert T, Buchheidt D, *et al.* Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients: guidelines of the infectious diseases working party of the German Society of Haematology and Oncology. *Eur J Cancer* 2009; 45: 2462–2472.
65. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006; 54: 628–634.
66. Reid AB, Chen SC, Worth LJ. *Pneumocystis jirovecii* pneumonia in non-HIV-infected patients: new risks and diagnostic tools. *Curr Opin Infect Dis* 2011; 24: 534–544.
67. Tasaka S, Tokuda H. *Pneumocystis jirovecii* pneumonia in non-HIV-infected patients in the era of novel immunosuppressive therapies. *J Infect Chemother* 2012; 18: 793–806.
68. Gan J, Manadan AM, Sequiera W, *et al.* Tuberculosis infections and tumor necrosis factor alpha antagonists. *Am J Ther* 2013; 20: 73–78.

Chapter 3

Microbiology of bacterial CAP using traditional and molecular techniques

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SUMMARY: In the setting of community-acquired pneumonia (CAP), the conventional microbiological workup is based on culture-based techniques and antigen testing, with a fundamental role in the identification, confirmation and contribution of antibiotic sensitivity of bacterial pathogens involved in its aetiology. However, this is the era of molecular testing and, certainly in past years, novel approaches based on nucleic acid amplification for detection, identification and quantification, as well as sequence-based techniques, have led to important improvements in the diagnosis or exclusion of certain diagnoses, and in the management and monitoring of lower respiratory tract infections. Such approaches attempt to provide accuracy, high sensitivity and specificity, and reduce the turnaround time. Phenotypic methods remain important in the diagnosis of bacterial CAP and molecular approaches, which are increasingly standardised and accessible, are being incorporated more frequently into the routine diagnostic workup.

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Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality among adults worldwide, and is one of the most common acute infections requiring hospital admission. According to previous reports, bacteria are the most common causative agents; however, the aetiology of CAP remains unknown in up to 50% of cases when traditional microbiological tests are performed [1–5]. Infection is usually only defined in hospital-managed cases. Molecular techniques have provided diagnostic sensitivity and modified the range of microorganisms which may be involved in CAP. However, they have also generated new questions about the role of the microorganisms detected in the pathogenesis of infection, and highlighted difficulties in interpreting the results.

This chapter aims to provide a general overview of the tools that are available for the microbiological diagnosis of bacterial CAP. Despite their limitations, culture-based techniques still dominate this field. Antigen testing and molecular methods, acting as culture-dependent or independent approaches, have proven their potential usefulness in the diagnosis of CAP. Despite the interest they generate, this chapter does not address issues related to CAP caused by *Mycobacterium tuberculosis* or in immunocompromised patients.

Causal microorganisms

In the aetiology of CAP there is important variability in the causal agent [6, 7], but bacteria continue to have a predominant role. Factors related to the population, and geographical and epidemiological data, as well as the methodology and resources applied for microbiological diagnosis, have an impact on the aetiological spectrum of this pathology [7].

In all fields *Streptococcus pneumoniae* is the most frequent causative agent [4, 6–8]. It is followed by atypical bacteria and some respiratory viruses, which are frequently detected simultaneously with *S. pneumoniae*. This suggests a pathogenesis of mixed infection, which still requires clarification. *Haemophilus influenzae* and *Moraxella catarrhalis* are more frequent in patients with chronic obstructive pulmonary disease and elderly patients with comorbidity [9]. *Staphylococcus aureus* is one of the least frequent agents in CAP [10]. Interest regarding this agent has increased in cases of resistant strains to methicillin or carriers of Panton–Valentine leukocidine [11]. Anaerobic bacteria have been described as a cause of CAP due to bronchoaspiration with a relatively low incidence of less than 5% [3, 5, 12]. The incidence of *Enterobacteriaceae* and *Pseudomonas aeruginosa* is low in hospitalised patients with CAP when healthcare-associated pneumonia cases are not considered [13]. The possibility of multidrug-resistant organisms, although less frequent in CAP, must also be suspected [14].

Legionella pneumophila and *Chlamydophila pneumoniae* are, together with *S. pneumococcus*, the bacterial agents most frequently involved in CAP [15]. *L. pneumophila* is increasingly recognised as a significant cause of isolated cases or CAP outbreaks. In this setting, diagnostic laboratory tests should be applied to all patients with pneumonia [16]. In addition, *Mycoplasma pneumoniae* is a frequent cause of CAP, mainly in the years in which there is a CAP epidemic [17]. CAP presenting as a low-severity disease particularly affects children and young adults [18]. Other atypical bacteria, such as *Coxiella burnetii* and *Chlamydophila psittaci*, are less common and are associated with epidemiological background [19, 20].

Other microorganisms, such as *M. tuberculosis* and atypical mycobacteria, and bioterrorism agents (such as *Bacillus anthracis*, *Francisella tularensis* and *Yersinia pestis*) are also causative pathogens of bacterial CAP and are associated with specific epidemiological conditions or risk factors [21].

Polymicrobial aetiology has been reported previously [2, 22, 23]. Incidence varies between 2% and 13% of cases depending on the diagnostic methods used and the intensity of the investigation for possible causative agents. In these cases it is difficult to identify the role of each diagnosed agent.

In CAP not requiring hospital admission the proportion of cases with atypical microorganisms is higher than in inpatients, while in patients requiring hospitalisation the most frequent aetiological agents are a diverse group of well-known bacterial and viral pathogens [1–8]. In relation to the cases of CAP requiring intensive care unit admission, apart from the common pathogens such as *S. pneumoniae*, multidrug-resistant pathogens should also be considered [24].

Clinical samples to be collected

According to the CAP management guidelines [21, 25, 26], while routine diagnostic tests could be optional in outpatients or patients hospitalised with mild cases of CAP, blood cultures, sputum staining and sputum culture should be carried out in hospitalised patients and in cases of severe CAP. In addition to blood culture and sputum samples or endotracheal aspirates in intubated patients, urinary antigen tests for *S. pneumoniae* and *L. pneumophila* are recommended. Table 1 summarises the scenarios in which the guidelines recommend microbiological diagnostic testing in CAP [21, 25].

Perhaps the most controversial sample is the sputum obtained for staining and cultures, due to the difficulty in obtaining expectorated sputum samples of adequate quality, which can lead to a low yield of bacterial cultures. Up to 50% of patients might have a non-productive cough and in 50% of those with productive cough the samples are contaminated with upper respiratory tract

Table 1. Scenarios in which the guidelines recommend microbiological diagnostic testing in community-acquired pneumonia

Hospitalised patients with specific clinical indication
Failure of outpatient antibiotic therapy
Severe obstructive or structural lung disease
Pleural effusion
Cavitary infiltrates
Positive pneumococcal or *Legionella* urinary antigen tests
Active alcoholism
Epidemiological factors or risk factors that suggest specific aetiologies
Legionnaires disease
MRSA/MDRO
Virus influenza: H1N1/H3N2/H5N1 (avian influenza)
Other viruses: SARS/MERS/Hantavirus
Bioterrorism agents (anthrax/tularaemia/plague)
Severe cases requiring ICU admission
Expectations of change of antimicrobial therapy according to results
Nonresponse to treatment
Worsening patient

MRSA: methicillin-resistant *Staphylococcus aureus*; MDRO: multidrug-resistant organisms; SARS: severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; ICU: intensive care unit.

secretions [27], despite the possibility that some pathogens may be part of the commensal flora. The samples obtained using bronchoscopic techniques provide more significant microbiological results for CAP compared to conventional sputum cultures [28]. Bronchoscopic indications in CAP (in immunocompetent patients) are often related to the presence of serious or slowly responding pneumonia, clinical deterioration or failure to stabilise [29, 30].

Respiratory specimens and serum can be collected in suspected cases of atypical pneumonia [31]; however, the need to obtain acute and convalescent specimens, the lack of sensitivity and specificity, and the delayed or retrospective results make serological tests inadequate for individual patient management, thus molecular tests prevail.

Another sample to consider in CAP is pleural fluid. When a significant pleural effusion is present, diagnostic thoracentesis should be performed. Bacterial pathogens detected in Gram stain or cultures from pleural fluid are usually a true reflection of the microbial cause of pneumonia [31].

Aetiological diagnosis based on current culture-based techniques and antigen testing

The use of cultures in respiratory samples or blood culture in the diagnosis of CAP is controversial due to their overall low yield and long turnaround time. Their sensitivity might be significantly reduced due to the use of antibiotics prior to sampling [29, 32, 33] and a positive result, including bacterial identification and the investigation of antibiotic sensitivity, which usually takes 48–72 h. There is a clear positive effect of culture isolation of potential pathogens in patient care, based on the epidemiological implications that might be involved. The possibility of knowing the antibiotic susceptibility patterns will allow selection of optimal antimicrobial therapy.

Respiratory cultures

Sputum stain and culture

For CAP diagnosis, the value of the sputum staining and culture results depend on the pre-test probability that the patient has bacterial pneumonia and the collection of pre-treated samples, as well as factors related to sampling and processing. Proper collection, transport and microscopic screening of sputum samples, based on the actual number of squamous epithelial cells and

polymorphonuclear leukocytes [34], can increase diagnostic accuracy and reduce the number of cultures performed, resulting in considerable cost saving. In addition, a predominant bacterial morphotype with the microbiota might suggest, with a variable sensitivity, the aetiological agent of pneumonia. In several studies Gram stain has been indicative of the pathogen [28, 35–37], mainly in cases where *S. pneumoniae* was isolated by culture, with sensitivity up to 82% for pneumococcal pneumonia and ~78% for staphylococcal pneumonia, *H. influenzae* or Gram-negative bacilli pneumonia, and specificity of 93–96% [35]. In the absence of prior antibiotic treatment, adequate sputum collection and observation of a predominant morphotype in the Gram stain can be useful in the diagnosis and recommendation of antimicrobial treatment [36]. In specific cases it has also been proven to be helpful as an early therapeutic indicator for the evaluation of the effectiveness of empiric therapy in CAP [38].

When using conventional cultures, namely blood agar, chocolate agar and MacConkey agar [39], a positive result including bacterial identification and the study of antibiotic sensitivity usually takes 48–72 h. However, the Gram stain result might be available in the first 2 h after sample collection. This certainly depends on the laboratory logistics and protocols of each health centre. This is not applicable when *Legionella* spp. is suspected to be the cause of the infection (fig. 1).

Endotracheal aspirates and invasive samples

In CAP, the culture yield is increased in endotracheal aspirates and samples obtained by bronchoscopy [21, 28]. Among them, endotracheal aspirates are the easiest and fastest samples to obtain in intubated patients. The processing and analysis of endotracheal aspirates is performed in a similar manner to sputum sampling [39]. These respiratory samples are usually cultured by qualitative and quantitative techniques. However, interpretation of the results improves when quantitative criteria are used in both bronchoscopic, *i.e.* sputum, and endotracheal aspirate samples [21], which helps to establish differences among contamination, colonisation or infection. Overall, quantitative cultures increase the diagnostic specificity, but sensitivity is dependent on the threshold chosen for a positive culture. The threshold bacterial count depends on the type of sample collected. A threshold for infection of $\geqslant 10^5$ CFU·mL^{-1} pathogen microorganisms in endotracheal aspirate, $\geqslant 10^4$ CFU·mL^{-1} in bronchoalveolar lavage (BAL) and $\geqslant 10^3$ CFU·mL^{-1} in protected brush specimen have been described [40–42]. In BAL samples this cut-off has reported a specificity of 100%, but has only been positive in one-third of adult patients with lower respiratory tract infection [42].

Negative cultures

In relation to the time taken to obtain a positive result, a negative result after 18–24 h of incubation can provide useful information for diagnosis and patient management. A negative

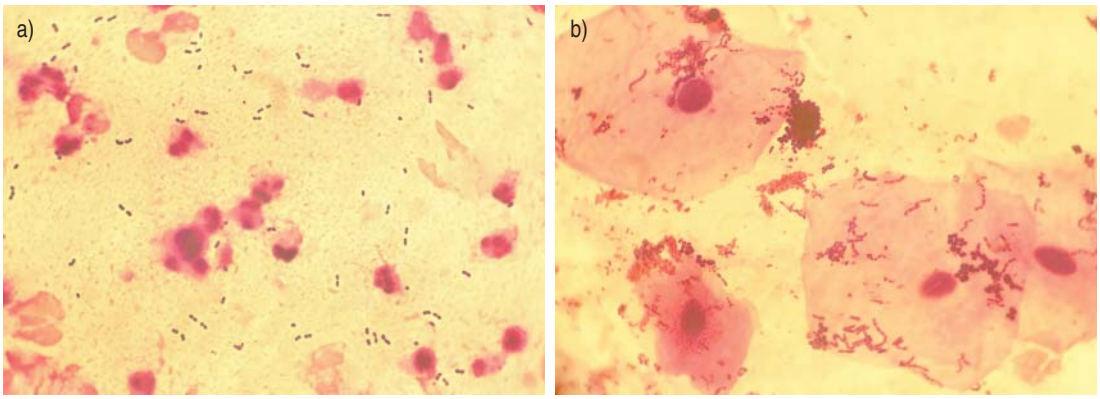

Figure 1. a) Gram staining (1000x) of a good quality sputum sample (group 4 or 5 of Murray and Washington's grading) showing monomicrobial flora. Gram-positive lancet-shaped diplococci are observed, suggestive of the genus *Streptococcus.* b) Gram staining (1000x) of a poor quality sputum sample (group 1 or 2 of Murray and Washington's grading) showing polybacterial flora.

bacterial culture does not exclude infectious aetiology in CAP and while a negative result can be caused by the use of an antimicrobial agent prior to sampling [29, 32, 33], it can also suggest the need to rule out other pathogens or non-bacterial pneumonia. This leads to the consideration of other diagnostic tests and the assessment of whether the spectrum of the prescribed antibiotic treatment is enough to ensure coverage of the possible agents involved.

Other cultures

Anaerobic cultures

The diagnosis of lung infection by anaerobes is often a presumptive diagnosis. Performing anaerobic culture of a respiratory sample is not standard practice in conventional cultures, except in the case of lung biopsies and pleural fluids. Recent sequence-based molecular tests have shown the presence of higher rates of anaerobic bacteria in BAL samples compared to cultures, suggesting it has a possible role in the aetiology of CAP [43].

Legionella *culture*

European data indicate that the proportion of cases of *Legionella* infection diagnosed by culture is low (9%) compared to those diagnosed by urinary antigen detection (81%) [44]. However, *Legionella* culture is the reference method for isolation of *Legionella* spp. because of its high specificity. Sputum sample is considered to be the best specimen for the isolation of these organisms in patients with pneumonia [31]. Culture on specific media (buffered charcoal yeast extract agar) should always be performed in addition to the antigen urinary test when legionellosis is suspected [45]. The main advantage of the culture is that all *Legionella* spp. can also be detected by this method. In addition, to confirm linked cases and the possible common environmental source, the standard serotyping of isolated cases and epidemiological genotyping in suspected case clusters or outbreaks requires prior isolation of the organism by culture [46]. Moreover, there are some drawbacks associated with the *Legionella* culture as it has low sensitivity, which varies with disease severity and is dependent on the skills of the laboratory staff [47]. Furthermore, patients with atypical pneumonia often do not produce sputum or, if they do, their sputum is frequently of poor quality. Although *Legionella* can be detected in these samples, the culture is often discarded by the laboratory. Another inherent problem with *Legionella* culture is the need to incubate it for several days because the organisms are slow growing. This limits its use in the early diagnosis and management of infection.

Blood cultures

These are recommended for hospitalised patients before antibiotic therapy is administered [21]. Under this condition blood cultures have a very high specificity but are positive in less than 20% of cases [48, 49]. Positivity is commonly associated with severe illness justifying their use. The relatively low positivity is an argument against using blood cultures. Benefits of blood cultures include the identification of possible causative agents, antimicrobial susceptibility testing and the estimation of the prognosis of the patient, which is eventually helpful for patient management [50]. Their value in mild-to-moderate CAP has been questioned [48] and predictive factors of positive blood culture have not been identified in outpatients, thus clinical judgment has to prevail in the decision as to whether to perform the test or not [51].

Antigen testing

In contrast to the methods discussed above which are laborious and time-consuming, the advantage of antigen detection is the possibility of setting up a prompt diagnosis. In CAP, antigen testing has been performed on respiratory specimens, serum and urine [52–54]. Respiratory samples are commonly used for respiratory virus antigen detection, and urine has become a successful means for quickly detecting bacterial pulmonary pathogens that are difficult to diagnose using culture-based techniques. Currently, commercial available techniques are based on the

immunofluorescence technique, and enzyme immunoassay (EIA) and immunochromatographic membrane (ICT) tests, which provide results with minutes or a few hours.

Legionella *urinary antigen detection*

In *L. pneumophila*, urinary antigen detection has proven to be the most helpful and rapid test for the diagnosis of *Legionella* infection, not only in the diagnosis of individual cases of *Legionella* pneumonia. It allows rapid screening of the cases, application of a specific antibiotic treatment at the onset of the disease and early identification of outbreaks, favouring early preventative measures. Its use is recommended for patients with suspected atypical pneumonia, epidemic risk factors, and pneumonia of unknown origin or therapeutic failure with β-lactam antibiotics [31].

Both EIA and ICT assays have been adapted for the effective detection of the soluble antigen of the *L. pneumophila* serogroup 1 cell wall. 85–90% of cases of Legionnaires diseases are caused by serogroup 1 [55]. There are several EIA tests commercially available; sensitivity using concentrated urine can reach 90% and specificity can reach 98–100% [56]. These techniques are presented in a standard 96 microwell breakaway format with a turnaround time of approximately 2.5 h. Meanwhile the ICT assays, which have been available since the end of the 1990s [57], are faster, technically less complex, can be made individually and produce results in 15 minutes or less, depending on the concentration of antigen in the urine. Sensitivity varies between 56% and 74% in non-concentrated urine samples, and up to 97% in concentrated urine, with 100% specificity in all cases [57–60]. The results are comparable with sensitivity and specificity of EIA techniques [58, 59].When various marketed ICT tests have been compared, the BinaxNOW test (Alere, Waltham, MA, USA) most frequently shows better results [58, 60, 61]. Some features to consider in its assessment are, among others, that: the antigenuria may persist for several weeks or months after the acute phase of the disease [56] so a positive result may suggest a current or past infection; a negative result makes *Legionella* infection unlikely but does not rule it out; the results are not influenced by the prior administration of antibiotics as sputum culture [58]; and it increases its sensitivity by additional readings at later time-points [59, 62].

Meta-analysis tests of *Legionella* urinary antigen (serogroup 1 and others) included 30 studies with six different diagnostic techniques. SHIMADA *et al.* [63] reported an excellent pooled specificity (99%) but only a moderate pooled sensitivity (74%), with a false-negative rate of more than 25%, a fact to take into account in the indication for treatment (prescription or stop) of antibiotics against *Legionella*.

Urinary antigen tests for *L. pneumophila* and *S. pneumoniae* have been recommended by the CAP management guidelines [21, 25, 26] and, to date, are routinely incorporated in the diagnostic testing of CAP.

Pneumococcal antigen detection

The antigen detection for the diagnosis of pneumococcal infection has been widely documented using a broad variety of diagnostic techniques [64–66], but none of them have been accepted in diagnosing CAP in general terms.

Just over a decade ago, an ICT test was developed to detect the cell wall antigen of *S. pneumoniae* in urine [67]. As for the detection of *Legionella* urinary antigen, this test is a rapid and simple ICT test providing results within a few minutes and detecting the C-polysaccharide cell wall antigen common to all *S. pneumoniae* strains [68].

The results of pneumococcal antigen detection in urine samples using ICT tests compared to traditional microbiological methods have reported sensitivity between 50% to 80% and specificity greater than 90% [54, 68–71]. A positive predictive value (PPV) greater than 90% and a negative predictive value (NPV) of 82% have been described previously [70]. A recent meta-analysis of 27 studies on urine pneumococcal antigen tests in hospitalised patients with suspected CAP described a pooled sensitivity of 74% and a pooled specificity of 97% [72]. The high sensitivity and specificity compared with the culture suggests that this test may be used in the diagnosis of

pneumococcal CAP without substituting sputum or blood cultures. The authors have emphasised the need for further work to assess the potential impact of this test in clinical practice, particularly in antibiotic stewardship programmes [72].

Among some of the problems described are the false-positive results in oropharyngeal pneumococcal carriage [73, 74], namely weak positive results caused by non-pneumococcal microorganisms [70, 75] and positive results for several weeks after the pneumonia onset [76]. The significance of positive ICT test results in patients with pneumonia without an identified pathogen by reference microbiological methods cannot be determined. They may indicate problems with specificity or a true-positive result of pneumococcal pneumonia undetected by standard microbiological methods. Colonisation status as a potential source of false-positive results requires further evaluation [75].

Recent studies are focusing not only on pneumococcal urinary antigen detection but also the possible serotypes involved in the infectious process through the combination of ICT tests and multiplex PCR urinary detection assay for the identification of vaccine pneumococcal serotypes [77].

New PCR-based approaches

Nucleic acid-based amplification methods have been, and will continue to be, the most commonly used methods in the molecular diagnosis of infectious diseases [78]. Species-specific PCR assays confer a greater level of sensitivity of detection compared to conventional culture-based diagnostics [79, 80]. They have become the standard method for the microbiological diagnosis of some respiratory diseases surpassing conventional procedures [80, 81].

Conventional PCR approaches are still complex due to the manual testing workflow, the time-consuming procedures and their specific requirements of special infrastructure and skilled staff. Novel real-time PCR-based platforms directed at respiratory infections or that are potentially useful in this pathology have been described [82, 83]. Some features, such as high sensitivity and specificity, short-term results, use of direct clinical samples, multiple targets leading to the identification and detection of antimicrobial-resistance determinants, and the option to obtain the microbial load by quantitative tests, make them useful diagnostic tools [82, 83].

PCR-based platforms that might offer useful information in less than 24 h

New real-time PCR platforms potentially applicable in bacterial CAP diagnosis are currently available. They offer rapid, accurate and reliable results that could help address antimicrobial treatment. In clinical practice, these methods are usually reserved for cases either requiring hospital admission or of poor prognosis.

Monomicrobial identification with or without antimicrobial resistance

The possibility of diagnosis is offered by an automated assay (Xpert MRSA/SA; Cepheid, Sunnyvale, CA, USA) validated for the detection of *S. aureus* and the simultaneous identification of antimicrobial resistance (*mecA* gene and staphylococcal cassette chromosome *mec* (SCC*mec*)). It consists of a random-access test of a single-use cartridge for automatic nucleic acid extraction, PCR amplification and real-time detection [84], starting from direct clinical specimens, with a less than 2 min hands-on time-frame and results within 1 h. These tests are aimed at nasal carrier screening, wound specimens and blood cultures [84, 85], but use with samples of the lower respiratory tract (endotracheal aspirates) in patients with nosocomial pneumonia have been recently reported [86]. Specifically in this case, the molecular test was conducted when Gram stain showed Gram-positive cocci suggesting the genus *Staphylococcus*. Compared with the quantitative culture, the results showed sensitivity, specificity, PPV and NPVs of 99%, 72%, 91% and 96%, respectively [86]. The authors used the Xpert MRSA/SA SSTI test (Cepheid), which has been approved (by the US Food and Drug Administration) for detection of *S. aureus* or

methicillin-resistant *S. aureus* (MRSA) in skin and soft tissue infection swabs [85]. The use of this test in respiratory secretions was off-label use.

Multiplex panels for respiratory bacteria and virus

Recently, a real-time PCR platform to diagnose lower respiratory tract infections, combining the same viral and bacterial detection assay (FilmArray RP-respiratory panel; BioFire Diagnostics, Salt Lake City, UT, USA) was made commercially available [87]. It is a molecular, multiplex respiratory pathogen panel available for the simultaneous detection of 17 respiratory viruses, as well as influenza A(H1N1)pdm09, plus three bacteria associated with CAP (*Bordetella pertussis*, *C. pneumoniae* and *M. pneumoniae*) [87, 88]. This test stands out for its large panel of respiratory pathogens in an integrated and closed diagnostic system. Starting from an unprocessed clinical sample, all steps, such as nucleic acid purification, reverse transcription, PCR amplification and melting curve analysis, occur in a single assay therefore minimising carry over contamination [87]. It is simple to use with minimal hand-on time and provides qualitative results in about 1 h. In addition, it has broad possibilities in the detection of other pathogens and in other types of clinical samples [89, 90]. For example, FilmArray Blood Culture panel can identify more than 25 pathogens, such as *S. pneumoniae*, *H. influenzae*, *S. aureus*, various *Enterobacteriaceae* and some non-fermenter bacilli, and four antibiotic resistance genes [90]. There might be other applications in development that address other uses of respiratory specimens for the detection of common bacterial pathogens associated with lower respiratory tract infection.

Comparative studies on FilmArray diagnostic performance in relation to other validated platforms for respiratory viruses have been described previously [91–94]. These studies have shown 100% specificity for all targets and variable sensitivity for each viral target, without benchmark results relating to bacterial detection.

Multiplex panel for respiratory bacteria

Another newly introduced platform aimed at diagnosing severe pneumonia (Unyvero P50 Pneumonia Cartridge; Curetis, Holzgerlingen, Germany) includes the detection and identification of 16 bacteria and one fungus responsible of more than 50% of severe non-viral pneumonia, and 23 antibiotic resistance markers. It is a random access, multiplex assay that allows the simultaneous amplification of nucleic acids in a closed system, providing qualitative results in about 4 h. Among its target organisms are *S. pneumoniae*, *H. influenzae*, *L. pneumophila* *C. pneumoniae*, *M. catarrhalis*, *S. aureus*, *Klebsiella pneumoniae*, *Escherichia coli*, other *Enterobacteriaceae*, some non-fermenter bacilli and *Pneumocystis jirovecii*. In its first clinical validation, the global data of sensitivity and specificity were 81% and 96%, respectively, in comparison to standard microbiology culture and sequencing results. The PPV for the detection of different markers of resistance, including markers of β-lactamase resistance, were 40–86%. In data related to bacterial identification, as well as in other markers of antibiotic resistance, a high heterogeneity of the results was identified [95].

PCR-based methods in bacterial quantification

Real-time PCR is well known for its ability to quantify molecular targets [96]. Technically, real-time quantitative PCR (qPCR) is performed using standards that have known or calibrated levels of target nucleic acid [97].

Various pathogens related to bacterial CAP have been subjected to quantitative studies by qPCR techniques [98–104]. Among the issues that arouse interest for microbiologists and clinicians are: the setting of molecular breakpoints on the bacterial load in different types of clinical samples that show an association with the clinical course of the infection process; the cut-offs on the bacterial load in respiratory samples that allow infection to be distinguished from colonisation; and in the case of detection of two or more respiratory pathogens (viruses and/or bacteria), determining the extent of participation of each one in the infective process based on their concentration.

The detection and quantification of bacterial and viral pathogens have been tested by qPCR in sputum samples from patients with chronic obstructive pulmonary disease during stable periods and acute exacerbations of the disease [105–107]. qPCR is more discriminatory at detecting typical bacteria than microbiological culture [107] and the threshold cut-off value of 10^{-5} CFU·mL^{-1} showed the best sensitivity, specificity, PPV and NPV for bacteria, *i.e. S. pneumoniae*, *S. aureus*, *Haemophilus* spp. and *M. catarrhalis*. With this value as the gold standard (100%), the sensitivity of culture for *S. pneumoniae* detection is approximately 50% [106].

Specifically in CAP, the results of pneumococcal load have been reported in sputum samples to help establish the aetiology [100], in nasopharyngeal specimens to distinguish pneumococcal CAP from asymptomatic colonisation [104], and in blood samples to determine an association with disease severity [98, 99]. Pneumococcal density $\geqslant$8000 copies·mL^{-1} in nasopharyngeal samples had a sensitivity and specificity of 82% and 92%, respectively, to differentiate pneumonia from colonisation; using that cut-off, the proportion of CAP cases attributable to *S. pneumoniae* increased from 27% to 53% [104]. Moreover, a quantification study of pneumococcal DNA load by qPCR was prospectively conducted on whole-blood samples in more than 300 patients with CAP. The molecular test exceeded the sensitivity of blood cultures for the detection of pneumococcal bacteraemia nearly twice, and 1000 copies·mL^{-1} *S. pneumoniae* DNA was detected upon patient admission which was associated with a statistically significant higher risk for shock and mortality [99]. Another study with a similar number of patients with CAP was in line with these findings regarding the association between the increase of pneumococcal load in serum and probably in urine with disease severity, but not with sputum. The authors suggest that the role of colonisation or the carrier status of *S. pneumoniae* in the interpretation of molecular results could be clarified by future studies on the bacterial load in respiratory samples [98].

PCR-based diagnostic methods available to date are helpful and, in some cases, have become the baseline method in the diagnosis of pneumonia due to their advantages in relation to culture.

16S sequencing in clinical microbiological lab

In clinical microbiology, identification based on molecular amplification and subsequent sequencing of 16S rRNA gene (16S sequencing) has primarily used the gene extracted from the pure bacterial cultures. However, a large number of microorganisms are barely cultivable or are uncultivable using routine microbiological diagnosis techniques [108], and in these cases 16S sequencing could enable bacteria identification directly from the clinical sample as a culture-independent approach [43, 109, 110].

Most molecular assays designed specifically for one or multiple organisms (*i.e.* singleplex or multiplex PCR) require predetermination of the likely microbial species present in a particular infection. They are performed under the assumption that the detection of a microorganism is sufficient to produce the suspected disease [111, 112]. This provides high sensitivity and specificity but detects only what is being investigated [112]. Identification based on universal targets has a different approach as there is no pre-established target bacteria species or genus, and identifies one or more possible causative agents by comparing a base sequence.

Culture-dependent approach

16S sequencing is currently used in clinical laboratories for bacterial strain identification of common species that show ambiguous biochemical profiles or strains with biochemical characteristics that are not adapted to any recognised species. This might lead to the description of new pathogens and the confirmation of uncommon bacteria [113].

Culture-independent approach

16S sequencing is commonly used from direct clinical samples from sterile body sites. A high concordance of more than 90% for 16S sequencing and routine bacterial culture has been reported

in a study with almost 400 specimens of various locations, indicating that the diagnostic performance of these techniques for acute bacterial infections is comparable to bacterial culture and useful for bacterial identification, even in patients pre-treated with antibiotics [109]. However, although direct identification from clinical samples is an extremely effective technique, it does not enable further characterisation of the infectious microorganisms [114], including the determination of susceptibility to various groups of microbial agents.

Specimens from sterile body sites/specimens with negative culture

Overall, the use of 16S sequencing in the laboratory routine as a culture-independent approach has been limited to specimens from sterile body sites or to those expected to be monobacterial infection [115–118]. In respiratory samples, this technique has been used in samples deemed "sterile", such as pleural fluids [119, 120] and lung biopsies obtained by transthoracic fine-needle aspiration [121], in patients with CAP.

Another clear indication of 16S sequencing from clinical samples is when bacterial infection is suspected despite the fact that the culture fails. In these cases, some authors have presented an algorithm based on 16S sequencing [109]. In this algorithm, samples from sterile body sites submitted to the microbiological laboratory are subjected to broad-range PCR if cultures (including enriched cultures) remained negative after 72 h of incubation. As mentioned previously, up to 50% of bacterial pathogens causing CAP are not identified using conventional cultivation methods [1–4]. The persistence of a negative culture might be caused by bacteria with special or fastidious culture [122, 123], simply non-cultivable bacteria [124], possible new pathogens [125, 126] or by the use of antibiotics before sampling (antibiotic treatment for more than 1 day prior to sample collection might result in a consistency reduction of 16S-positive culture superior to 40%) [127].

A study on the use of 16S sequencing in routine diagnostic workup in a clinical microbiology laboratory with 382 samples including blood samples, BAL specimens, pleural fluids, and others tissues and fluids, provided the sole evidence of the presence of specific bacterial DNA in 70 out of 275 culture negative specimens; 58 of these were considered to be clinically significant pathogens. The most common agent detected by PCR only was *S. pneumoniae*, which might be difficult to isolate by culture due its tendency to undergo autolysis [112]. More recently, in 231 out of 394 specimens with a negative culture result, 16S sequencing showed 43% sensitivity and 100% specificity with a PPV and NPV of 100% and 80%, respectively, for culture-negative infections; an increase in NPV of up to 99% was observed for patients who had not been pre-treated prior to sampling. Most of the specimens came from nonsterile locations and most of the identified pathogens were common bacteria that usually grow in common culture media [109].

The increase in the detection rate of bacteria that are infrequently associated with the aetiology of CAP, such as oral streptococci and anaerobes, is one of the effects observed with the use of 16S sequencing in respiratory samples with negative culture. In a recent publication, 16% of anaerobic bacteria, such as *Prevotella* spp. and *Fusobacterium* spp., were detected in BAL samples of patients with CAP [43] compared with less than 5.5% when conventional methods were used [3, 128]. This suggests that bacterial species, other than the most common ones, should be considered as primary bacteria responsible for infection with unknown pathogens [43].

Although 16S sequencing is reasonably accurate for the detection of bacterial pathogens, the results are difficult to interpret when the corresponding culture is negative, the results detect an unusual pathogen and the sequence results indicate a mixed infection [109, 127, 129]. For the DNA analysis obtained directly from the clinical sample, material from sterile body sites is usually recommended [112, 127].

Specimens with mixed flora

The assessment of 16S sequencing performance results directly from polybacterial clinical specimens, as is the case with most of respiratory samples, is one of the leading challenges to address in this field. Despite showing a higher consistency of 16S sequencing-positive culture in

polymicrobial samples [43, 109, 127], results are difficult to interpret [127, 129, 130]. Ambiguous or low-specificity sequences are often overlooked and only the dominant bacterial sequences can be identified [127].

In a recent evaluation study of the bacteriological causes of CAP using 16S sequencing compared with conventional culture of BAL and sputum specimens, all samples showed a polymicrobial profile despite the measures adopted to avoid contamination by oral flora. The detection of a predominant microorganism (comprising over 80% of the detected bacteria) identified at species level was reached in about 50% of the samples; common bacterial pathogens of CAP such as *S. pneumoniae*, *M. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus* and some anaerobes were detected. In general, obligate anaerobes and oral streptococci were detected considerably more frequently using the molecular method than culture. These microorganisms are beginning to be considered as possible causatives agents in CAP patients [43]. However, future studies that dismiss their role as colonising or contaminating agents from the oropharynx and confirm their implication in the aetiology of this pathology are necessary.

Just as 16S sequencing can contribute to the detection of species not found by culture, some of the cultured bacteria are not found by sequencing. The latter is not rare in mixed samples, where all bacteria will be competing for the same reagents and those present at the lowest concentrations might be outcompeted in the PCR and not visible in the resulting sequencing chromatogram [127].

In the study of bacterial communities

16S rRNA gene sequencing has proven to be useful in bacterial identification, but in recent years it has been overshadowed by the rich information provided by metagenomic and whole microbial genome sequencing techniques [131, 132]. The information provided by these techniques is changing the opinion of: the host–pathogen relationship in infectious diseases with unclear aetiology; diseases that were not thought to have a microbial aetiology; and the role of the immune system in the infectious process [133]. These methods also have several limitations due to the resources and time required [134]. Targeted massive parallel sequencing of the 16S rRNA gene is more manageable and feasible to carry out and, despite the fact that it provides limited genotypic information, allows the phylotypic classification of bacterial species [135]. Deep sequencing of 16S rRNA has also been used in numerous studies of metagenomics to catalogue the taxonomic composition of the normal human microbiota [135, 136], and to explore how resident bacterial communities change during the various disease phases [131]. Due to this, bacterial diversity in the respiratory sphere has been specifically studied in the case of chronic respiratory pathology, *e.g.* chronic obstructive pulmonary disease [137] and cystic fibrosis [138].

The development of high-throughput next-generation sequencing technologies [139], applied to the products of the amplification of the 16S rRNA gene, has improved the creation of polymicrobial complex profiles through the analysis of sequences [137, 138, 140]. The characteristics of these technologies (increasing length, accuracy and number of readings generated) make it a suitable tool for studying the human microbiota in both healthy and diseased states. Despite the usefulness of the information that they provide, the main obstacles to their mainstream use are cost, the turnaround time for results, analytical complexity, scarcity of user-friendly platforms with clinical approach, and lack of experience in genomics. However, due to their potential impact on improved patient care, major changes in these molecular tests can be expected in the forthcoming years.

Conclusions

Bacterial CAP is one of the most frequent causes of hospital admission and microbiological diagnosis is still a matter of concern. Key issues in pathology management are the numerous cases in which the aetiological diagnosis is not achieved, despite an intensive search through commonly available laboratory methods, and turnaround time of microbiological results to address antibiotic therapy. With *S. pneumoniae* leading the different causative agents, its aetiological spectrum is

broad and includes numerous agents, some that are difficult to diagnose by traditional microbiological techniques. Culture-based methods continue to be fundamental for the diagnosis of bacterial CAP despite their long turnaround time, although their results are dependent on multiple factors, such as the cultivable character of the possible causative agents or the use of antimicrobial therapy prior to the sample collection. However, for many fastidious or uncultivable organisms, diagnosis tools other than culture should be used. Culture-independent techniques that are accurate and easy to perform and offer a short turnaround time, such as the urine antigen detection and molecular methods, complement the currently available conventional microbiology in CAP without providing a final solution in the microbiological diagnosis. Methods based on real-time PCR are those used most in the identification of microorganisms, as well as determinants of antimicrobial resistance and universal gene sequencing. The use of these tools as culture-independent methods in the microbiological diagnosis of infectious diseases will generally increase in the coming years. Due, not only to the continuous development of new user-friendly multiplexing platforms that detect viral and bacterial targets and resistance genes from clinical samples and that provide results in a few hours, but also to the development of technologies of high-throughput sequencing that allow genomic analysis to be incorporated beyond the field of research.

Statement of Interest

None declared.

References

1. Cilloniz C, Ewig S, Polverino E, *et al.* Microbial aetiology of community-acquired pneumonia and its relation to severity. *Thorax* 2011; 66: 340–346.
2. Johansson N, Kalin M, Tiveljung-Lindell A, *et al.* Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. *Clin Infect Dis* 2010; 50: 202–209.
3. Saito A, Kohno S, Matsushima T, *et al.* Prospective multicenter study of the causative organisms of community-acquired pneumonia in adults in Japan. *J Infect Chemother* 2006; 12: 63–69.
4. Lim WS, Macfarlane JT, Boswell TC, *et al.* Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. *Thorax* 2001; 56: 296–301.
5. Ruiz M, Ewig S, Marcos MA, *et al.* Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. *Am J Respir Crit Care Med* 1999; 160: 397–405.
6. Howard LS, Sillis M, Pasteur MC, *et al.* Microbiological profile of community-acquired pneumonia in adults over the last 20 years. *J Infect* 2005; 50: 107–113.
7. Woodhead M. Community-acquired pneumonia in Europe: causative pathogens and resistance patterns. *Eur Respir J* 2002; 20: Suppl. 36, 20s–27s.
8. File TM. Community-acquired pneumonia. *Lancet* 2003; 362: 1991–2001.
9. Reissig A, Mempel C, Schumacher U, *et al.* Microbiological diagnosis and antibiotic therapy in patients with community-acquired pneumonia and acute COPD exacerbation in daily clinical practice: comparison to current guidelines. *Lung* 2013; 191: 239–246.
10. Vardakas KZ, Matthaiou DK, Falagas ME. Incidence, characteristics and outcomes of patients with severe community acquired-MRSA pneumonia. *Eur Respir J* 2009; 34: 1148–1158.
11. Kreienbuehl L, Charbonney E, Eggimann P. Community-acquired necrotizing pneumonia due to methicillin-sensitive *Staphylococcus aureus* secreting Panton-Valentine leukocidin: a review of case reports. *Ann Intensive Care* 2011; 1: 52.
12. Cilloniz C, Ewig S, Ferrer M, *et al.* Community-acquired polymicrobial pneumonia in the intensive care unit: aetiology and prognosis. *Crit Care* 2011; 15: R209.
13. von Baum H, Welte T, Marre R, *et al.* Community-acquired pneumonia through *Enterobacteriaceae* and *Pseudomonas aeruginosa*: diagnosis, incidence and predictors. *Eur Respir J* 2010; 35: 598–605.
14. Fleming V, Buck B, Nix N, *et al.* Community-acquired pneumonia with risk for drug-resistant pathogens. *South Med J* 2013; 106: 209–216.
15. Sopena N, Sabria M, Pedro-Botet ML, *et al.* Prospective study of community-acquired pneumonia of bacterial etiology in adults. *Eur J Clin Microbiol Infect Dis* 1999; 18: 852–858.
16. Carratala J, Garcia-Vidal C. An update on *Legionella. Curr Opin Infect Dis* 2010; 23: 152–157.
17. Lenglet A, Herrador Z, Magiorakos AP, *et al.* Surveillance status and recent data for *Mycoplasma pneumoniae* infections in the European Union and European Economic Area, January 2012. *Euro Surveill* 2012; 17: pii, 20075.
18. Torres A, Rello J. Update in community-acquired and nosocomial pneumonia 2009. *Am J Respir Crit Care Med* 2010; 181: 782–787.

19. Marrie TJ. Q fever pneumonia. *Infect Dis Clin North Am* 2010; 24: 27–41.
20. Gacouin A, Revest M, Letheulle J, *et al.* Distinctive features between community-acquired pneumonia (CAP) due to *Chlamydophila psittaci* and CAP due to *Legionella pneumophila* admitted to the intensive care unit (ICU). *Eur J Clin Microbiol Infect Dis* 2012; 31: 2713–2718.
21. Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44: Suppl. 2, S27–S72.
22. Gencay M, Roth M, Christ-Crain M, *et al.* Single and multiple viral infections in lower respiratory tract infection. *Respiration* 2010; 80: 560–567.
23. de Roux A, Ewig S, Garcia E, *et al.* Mixed community-acquired pneumonia in hospitalised patients. *Eur Respir J* 2006; 27: 795–800.
24. Cilloniz C, Polverino E, Ewig S, *et al.* Impact of age and comorbidity on etiology and outcome in community-acquired pneumonia. *Chest* 2013; 144: 999–1007.
25. Lim WS, Baudouin SV, George RC, *et al.* BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; 64: Suppl. 3, iii1–iii55.
26. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections – full version. *Clin Microbiol Infect* 2011; 17: Suppl. 6, E1–59.
27. Ewig S, Schlochtermeier M, Goke N, *et al.* Applying sputum as a diagnostic tool in pneumonia: limited yield, minimal impact on treatment decisions. *Chest* 2002; 121: 1486–1492.
28. Manali E, Papadopoulos A, Tsiodras S, *et al.* The impact on community acquired pneumonia empirical therapy of diagnostic bronchoscopic techniques. *Scand J Infect Dis* 2008; 40: 286–292.
29. Hohenthal U, Sipila J, Vainionpaa R, *et al.* Diagnostic value of bronchoalveolar lavage in community-acquired pneumonia in a routine setting: a study on patients treated in a Finnish university hospital. *Scand J Infect Dis* 2004; 36: 198–203.
30. Menendez R, Torres A Treatment failure in community-acquired pneumonia, *Chest* 2007; 132: 1348–1355.
31. Loens K, Van Heirstraeten L, Malhotra-Kumar S, *et al.* Optimal sampling sites and methods for detection of pathogens possibly causing community-acquired lower respiratory tract infections. *J Clin Microbiol* 2009; 47: 21–31.
32. Resti M, Micheli A, Moriondo M, *et al.* Comparison of the effect of antibiotic treatment on the possibility of diagnosing invasive pneumococcal disease by culture or molecular methods: a prospective, observational study of children and adolescents with proven pneumococcal infection. *Clin Ther* 2009; 31: 1266–1273.
33. Liu YF, Gao Y, Chen MF, *et al.* Etiological analysis and predictive diagnostic model building of community-acquired pneumonia in adult outpatients in Beijing, China. *BMC Infect Dis* 2013; 13: 309.
34. Murray PR, Washington JA. Microscopic and baceriologic analysis of expectorated sputum. *Mayo Clin Proc* 1975; 50: 339–344.
35. Anevlavis S, Petroglou N, Tzavaras A, *et al.* A prospective study of the diagnostic utility of sputum Gram stain in pneumonia. *J Infect* 2009; 59: 83–89.
36. Roson B, Carratala J, Verdaguer R, *et al.* Prospective study of the usefulness of sputum Gram stain in the initial approach to community-acquired pneumonia requiring hospitalization. *Clin Infect Dis* 2000; 31: 869–874.
37. Miyashita N, Shimizu H, Ouchi K, *et al.* Assessment of the usefulness of sputum Gram stain and culture for diagnosis of community-acquired pneumonia requiring hospitalization. *Med Sci Monit* 2008; 14: CR171–CR176.
38. Fujisaki R, Yamaoka T, Yamamura M, *et al.* Usefulness of gram-stained sputum obtained just after administration of antimicrobial agents as the earliest therapeutic indicator for evaluating the effectiveness of empiric therapy in community-acquired pneumonia caused by pneumococcus or *Moraxella catarrhalis. J Infect Chemother* 2013; 19: 517–523.
39. York MK, Gilligan P, Church DL. Lower respiratory tract cultures. *In:* Garcia LS, ed. Clinical Microbiology Procedures Handbook. 3rd Edn. Washington DC, American Society for Microbiology, 2010; pp. 3.11.2.1–3.11.2.20.
40. Bouza E, Torres MV, Burillo A. Aportación del laboratorio de microbiología al diagnóstico de la neumonía asociada a la ventilación mecánica [The contribution of the microbiology laboratory to the diagnosis of ventilator-associated pneumonia]. *Enferm Infect Microbiol Clin* 2005; 23: Suppl. 3, 2–9.
41. Ruiz M, Torres A, Ewig S, *et al.* Noninvasive *versus* invasive microbial investigation in ventilator-associated pneumonia: evaluation of outcome. *Am J Respir Crit Care Med* 2000; 162: 119–125.
42. Rasmussen TR, Korsgaard J, Moller JK, *et al.* Quantitative culture of bronchoalveolar lavage fluid in community-acquired lower respiratory tract infections. *Respir Med* 2001; 95: 885–890.
43. Yamasaki K, Kawanami T, Yatera K, *et al.* Significance of anaerobes and oral bacteria in community-acquired pneumonia. *PLoS One* 2013; 8: e63103.
44. Joseph CA, Ricketts KD. Legionnaires disease in Europe 2007–2008. *Euro Surveill* 2010; 15: 19493.
45. Lamoth F, Greub G. Fastidious intracellular bacteria as causal agents of community-acquired pneumonia. *Expert Rev Anti Infect Ther* 2010; 8: 775–790.
46. Blyth CC, Adams DN, Chen SC. Diagnostic and typing methods for investigating *Legionella* infection. *NSW Public Health Bull* 2009; 20: 157–161.
47. Murdoch DR. Diagnosis of *Legionella* infection. *Clin Infect Dis* 2003; 36: 64–69.

48. Waterer GW, Wunderink RG. The influence of the severity of community-acquired pneumonia on the usefulness of blood cultures. *Respir Med* 2001; 95: 78–82.
49. Bishara J, Leibovici L, Ashkenazi S, *et al.* Seven-year study of bacteraemic pneumonia in a single institution. *Eur J Clin Microbiol Infect Dis* 2000; 19: 926–931.
50. Ishikawa G, Nishimura N, Kitamura A, *et al.* Impact of blood cultures on the changes of treatment in hospitalised patients with community-acquired pneumonia. *Open Respir Med J* 2013; 7: 60–66.
51. Marrie TJ. Blood cultures in ambulatory patients who are discharged from emergency with community-acquired pneumonia. *Can J Infect Dis* 2004; 15: 21–24.
52. Jacobs JA, Stobberingh EE, Cornelissen EI, *et al.* Detection of *Streptococcus pneumoniae* antigen in bronchoalveolar lavage fluid samples by a rapid immunochromatographic membrane assay. *J Clin Microbiol* 2005; 43: 4037–4040.
53. Dominguez J, Andreo F, Blanco S, *et al.* Rapid detection of pneumococcal antigen in serum samples for diagnosing pneumococcal pneumonia. *J Infect* 2006; 53: 21–24.
54. Genne D, Siegrist HH, Lienhard R. Enhancing the etiologic diagnosis of community-acquired pneumonia in adults using the urinary antigen assay (Binax NOW). *Int J Infect Dis* 2006; 10: 124–128.
55. Muder RR, Yu VL. Infection due to *Legionella* species other than *L. pneumophila. Clin Infect Dis* 2002; 35: 990–998.
56. Ruf B, Schurmann D, Horbach I, *et al.* Prevalence and diagnosis of *Legionella pneumonia*: a 3-year prospective study with emphasis on application of urinary antigen detection. *J Infect Dis* 1990; 162: 1341–1348.
57. Dominguez J, Gali N, Matas L, *et al.* Evaluation of a rapid immunochromatographic assay for the detection of *Legionella* antigen in urine samples. *Eur J Clin Microbiol Infect Dis* 1999; 18: 896–898.
58. Munoz MJ, Martinez Toldos MC, Yague G, *et al.* Evaluation of three immunochromatographic assays for detection of *Legionella pneumophila* serogroup 1 antigen in urine samples. *Rev Esp Quimioter* 2009; 22: 207–209.
59. Helbig JH, Uldum SA, Luck PC, *et al.* Detection of *Legionella pneumophila* antigen in urine samples by the BinaxNOW immunochromatographic assay and comparison with both Binax *Legionella* Urinary Enzyme Immunoassay (EIA) and Biotest *Legionella* Urin Antigen EIA. *J Med Microbiol* 2001; 50: 509–516.
60. Bruin JP, Diederen BM. Evaluation of Meridian TRU Legionella®, a new rapid test for detection of *Legionella pneumophila* serogroup 1 antigen in urine samples. *Eur J Clin Microbiol Infect Dis* 2013; 32: 333–334.
61. Diederen BM, Peeters MF. Evaluation of two new immunochromatographic assays (Rapid U *Legionella* antigen test and SD Bioline *Legionella* antigen test) for detection of *Legionella* pneumophila serogroup 1 antigen in urine. *J Clin Microbiol* 2006; 44: 2991–2993.
62. Held J. Increasing the sensitivity of the BinaxNOW Legionella urinary antigen immunochromatographic test by additional readings at later time points. *J Med Microbiol* 2012; 61: 884–885.
63. Shimada T, Noguchi Y, Jackson JL, *et al.* Systematic review and metaanalysis: urinary antigen tests for Legionellosis. *Chest* 2009; 136: 1576–1585.
64. Boersma WG, Lowenberg A, Holloway Y, *et al.* Pneumococcal capsular antigen detection and pneumococcal serology in patients with community acquired pneumonia. *Thorax* 1991; 46: 902–906.
65. Cerosaletti KM, Roghmann MC, Bentley DW Comparison of latex agglutination, counter immunoelectrophoresis for the detection of pneumococcal antigen in elderly pneumonia patients. *J Clin Microbiol* 1985; 22: 553–557.
66. Ericsson CH, Hallander HO, Rosen A, *et al.* Routine use of counterimmunoelectrophoresis for the detection of pneumococcal antigen in sputum. *Med Microbiol Immunol* 1986; 175: 241–249.
67. Dominguez J, Gali N, Blanco S, *et al.* Detection of *Streptococcus pneumoniae* antigen by a rapid immunochromatographic assay in urine samples. *Chest* 2001; 119: 243–249.
68. Murdoch DR, Laing RT, Mills GD, *et al.* Evaluation of a rapid immunochromatographic test for detection of *Streptococcus pneumoniae* antigen in urine samples from adults with community-acquired pneumonia. *J Clin Microbiol* 2001; 39: 3495–3498.
69. Roson B, Fernandez-Sabe N, Carratala J, *et al.* Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. *Clin Infect Dis* 2004; 38: 222–226.
70. Ishida T, Hashimoto T, Arita M, *et al.* A 3-year prospective study of a urinary antigen-detection test for *Streptococcus pneumoniae* in community-acquired pneumonia: utility and clinical impact on the reported etiology. *J Infect Chemother* 2004; 10: 359–363.
71. Gutierrez F, Masia M, Rodriguez JC, *et al.* Evaluation of the immunochromatographic Binax NOW assay for detection of *Streptococcus pneumoniae* urinary antigen in a prospective study of community-acquired pneumonia in Spain. *Clin Infect Dis* 2003; 36: 286–292.
72. Sinclair A, Xie X, Teltscher M, *et al.* Systematic review and meta-analysis of a urine-based pneumococcal antigen test for diagnosis of community-acquired pneumonia caused by *Streptococcus pneumoniae. J Clin Microbiol* 2013; 51: 2303–2310.
73. Tzeng DH, Lee YL, Lin YH, *et al.* Diagnostic value of the Binax NOW assay for identifying a pneumococcal etiology in patients with respiratory tract infection. *J Microbiol Immunol Infect* 2006; 39: 39–44.
74. Dowell SF, Garman RL, Liu G, *et al.* Evaluation of Binax NOW, an assay for the detection of pneumococcal antigen in urine samples, performed among paediatric patients. *Clin Infect Dis* 2001; 32: 824–825.
75. Porcel JM, Ruiz-Gonzalez A, Falguera M, *et al.* Contribution of a pleural antigen assay (Binax NOW) to the diagnosis of pneumococcal pneumonia. *Chest* 2007; 131: 1442–1447.

76. Marcos MA, Jimenez de Anta MT, de la Bellacasa JP et al. Rapid urinary antigen test for diagnosis of pneumococcal community-acquired pneumonia in adults. *Eur Respir J* 2003; 21: 209–214.
77. Huijts SM, Pride MW, Vos JM, *et al.* Diagnostic accuracy of a serotype specific antigen test in community-acquired pneumonia. *Eur Respir J* 2013; 42: 1283–1290.
78. Tenover FC. Developing molecular amplification methods for rapid diagnosis of respiratory tract infections caused by bacterial pathogens. *Clin Infect Dis* 2011; 52: Suppl. 4, S338–S345.
79. Azzari C, Moriondo M, Indolfi G, *et al.* Molecular detection methods and serotyping performed directly on clinical samples improve diagnostic sensitivity and reveal increased incidence of invasive disease by *Streptococcus pneumoniae* in Italian children. *J Med Microbiol* 2008; 57: 1205–1212.
80. Abu Raya B, Bamberger E, Gershtein R, *et al.* The laboratory diagnosis of *Bordetella pertussis* infection: a comparison of semi-nested PCR and real-time PCR with culture. *Eur J Clin Microbiol Infect Dis* 2012; 31: 619–622.
81. Jernigan DB, Lindstrom SL, Johnson JR, *et al.* Detecting 2009 pandemic influenza A (H1N1) virus infection: availability of diagnostic testing led to rapid pandemic response. *Clin Infect Dis* 2011; 52: Suppl. 1, S36–S43.
82. Caliendo AM. Multiplex PCR and emerging technologies for the detection of respiratory pathogens. *Clin Infect Dis* 2011; 52: Suppl. 4, S326–S330.
83. Endimiani A, Hujer KM, Hujer AM, *et al.* Are we ready for novel detection methods to treat respiratory pathogens in hospital-acquired pneumonia? *Clin Infect Dis* 2011; 52: Suppl. 4, S373–S383.
84. Wolk DM, Struelens MJ, Pancholi P, *et al.* Rapid detection of *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA) in wound specimens and blood cultures: multicenter preclinical evaluation of the Cepheid Xpert MRSA/SA skin and soft tissue and blood culture assays. *J Clin Microbiol* 2009; 47: 823–826.
85. Wolk DM, Picton E, Johnson D, *et al.* Multicenter evaluation of the Cepheid Xpert methicillin-resistant *Staphylococcus aureus* (MRSA) test as a rapid screening method for detection of MRSA in nares. *J Clin Microbiol* 2009; 47: 758–764.
86. Cercenado E, Marin M, Burillo A, *et al.* Rapid detection of *Staphylococcus aureus* in lower respiratory tract secretions from patients with suspected ventilator-associated pneumonia: evaluation of the Cepheid Xpert MRSA/SA SSTI assay. *J Clin Microbiol* 2012; 50: 4095–4097.
87. Poritz MA, Blaschke AJ, Byington CL, *et al.* FilmArray, an automated nested multiplex PCR system for multi-pathogen detection: development and application to respiratory tract infection. *PLoS One* 2011; 6: e26047.
88. Popowitch EB, O'Neill SS, Miller MB. Comparison of the Biofire FilmArray RP, Genmark eSensor RVP, Luminex xTAG RVPv1, and Luminex xTAG RVP fast multiplex assays for detection of respiratory viruses. *J Clin Microbiol* 2013; 51: 1528–1533.
89. Seiner DR, Colburn HA, Baird C, *et al.* Evaluation of the FilmArray® system for detection of *Bacillus anthracis*, *Francisella tularensis* and *Yersinia pestis*. *J Appl Microbiol* 2013; 114: 992–1000.
90. Blaschke AJ, Heyrend C, Byington CL, *et al.* Rapid identification of pathogens from positive blood cultures by multiplex polymerase chain reaction using the FilmArray system. *Diagn Microbiol Infect Dis* 2012; 74: 349–355.
91. Van Wesenbeeck L, Meeuws H, Van Immerseel A, *et al.* Comparison of the FilmArray RP, Verigene RV+, and Prodesse ProFLU+/FAST+ multiplex platforms for detection of influenza viruses in clinical samples from the 2011–2012 influenza season in Belgium. *J Clin Microbiol* 2013; 51: 2977–2985.
92. Hayden RT, Gu Z, Rodriguez A, *et al.* Comparison of two broadly multiplexed PCR systems for viral detection in clinical respiratory tract specimens from immunocompromised children. *J Clin Virol* 2012; 53: 308–313.
93. Rand KH, Rampersaud H, Houck HJ. Comparison of two multiplex methods for detection of respiratory viruses: FilmArray RP and xTAG RVP. *J Clin Microbiol* 2011; 49: 2449–2453.
94. Loeffelholz MJ, Pong DL, Pyles RB, *et al.* Comparison of the FilmArray Respiratory Panel and Prodesse real-time PCR assays for detection of respiratory pathogens. *J Clin Microbiol* 2011; 49: 4083–4088.
95. Klein M, Barth S, Burrack-Lange S, *et al.* First clinical validation of a rapid molecular test the Unyvero™ P50 Pneumonia Application detecting microorganisms and antibiotic resistance in patients with suspected severe pneumonia. ECCMID 2013, poster P1781.
96. Mackay IM. Real-time PCR in the microbiology laboratory. *Clin Microbiol Infect* 2004; 10: 190–212.
97. Espy MJ, Uhl JR, Sloan LM, *et al.* Real-time PCR in clinical microbiology: applications for routine laboratory testing. *Clin Microbiol Rev* 2006; 19: 165–256.
98. Werno AM, Anderson TP, Murdoch DR Association between pneumococcal load, disease severity in adults with pneumonia. *J Med Microbiol* 2012; 61: 1129–1135.
99. Rello J, Lisboa T, Lujan M, *et al.* Severity of pneumococcal pneumonia associated with genomic bacterial load. *Chest* 2009; 136: 832–840.
100. Johansson N, Kalin M, Giske CG, *et al.* Quantitative detection of *Streptococcus pneumoniae* from sputum samples with real-time quantitative polymerase chain reaction for etiologic diagnosis of community-acquired pneumonia. *Diagn Microbiol Infect Dis* 2008; 60: 255–261.
101. Abdeldaim GM, Stralin K, Olcen P, *et al.* Quantitative *fucK* gene polymerase chain reaction on sputum and nasopharyngeal secretions to detect *Haemophilus influenzae* pneumonia. *Diagn Microbiol Infect Dis* 2013; 76: 141–146.
102. Maurin M, Hammer L, Gestin B, *et al.* Quantitative real-time PCR tests for diagnostic and prognostic purposes in cases of legionellosis. *Clin Microbiol Infect* 2010; 16: 379–384.

103. Welti M, Jaton K, Altwegg M, *et al.* Development of a multiplex real-time quantitative PCR assay to detect *Chlamydia pneumoniae*, *Legionella pneumophila* and *Mycoplasma pneumoniae* in respiratory tract secretions. *Diagn Microbiol Infect Dis* 2003; 45: 85–95.
104. Albrich WC, Madhi SA, Adrian PV, *et al.* Use of a rapid test of pneumococcal colonization density to diagnose pneumococcal pneumonia. *Clin Infect Dis* 2012; 54: 601–609.
105. Sethi S. Molecular diagnosis of respiratory tract infection in acute exacerbations of chronic obstructive pulmonary disease. *Clin Infect Dis* 2011; 52: Suppl. 4, S290–S295.
106. Curran T, Coyle PV, McManus TE, *et al.* Evaluation of real-time PCR for the detection and quantification of bacteria in chronic obstructive pulmonary disease. *FEMS Immunol Med Microbiol* 2007; 50: 112–118.
107. Garcha DS, Thurston SJ, Patel AR, *et al.* Changes in prevalence and load of airway bacteria using quantitative PCR in stable and exacerbated COPD. *Thorax* 2012; 67: 1075–1080.
108. Rappe MS, Giovannoni SJ. The uncultured microbial majority. *Annu Rev Microbiol* 2003; 57: 369–394.
109. Rampini SK, Bloemberg GV, Keller PM, *et al.* Broad-range 16S rRNA gene polymerase chain reaction for diagnosis of culture-negative bacterial infections. *Clin Infect Dis* 2011; 53: 1245–1251.
110. Sontakke S, Cadenas MB, Maggi RG, *et al.* Use of broad range16S rDNA PCR in clinical microbiology. *J Microbiol Methods* 2009; 76: 217–225.
111. Rogers GB, Carroll MP, Bruce KD. Studying bacterial infections through culture-independent approaches. *J Med Microbiol* 2009; 58: 1401–1418.
112. Harris KA, Hartley JC. Development of broad-range 16S rDNA PCR for use in the routine diagnostic clinical microbiology service. *J Med Microbiol* 2003; 52: 685–691.
113. Clarridge JE 3rd. Impact of 16S rRNA gene sequence analysis for identification of bacteria on clinical microbiology and infectious diseases. *Clin Microbiol Rev* 2004; 17: 840–862.
114. Patel JB. 16S rRNA gene sequencing for bacterial pathogen identification in the clinical laboratory. *Mol Diagn* 2001; 6: 313–321.
115. Kotilainen P, Jalava J, Meurman O, *et al.* Diagnosis of meningococcal meningitis by broad-range bacterial PCR with cerebrospinal fluid. *J Clin Microbiol* 1998; 36: 2205–2209.
116. Arosio M, Nozza F, Rizzi M, *et al.* Evaluation of the MicroSeq 500 16S rDNA-based gene sequencing for the diagnosis of culture-negative bacterial meningitis. *New Microbiol* 2008; 31: 343–349.
117. Marin M, Munoz P, Sanchez M, *et al.* Molecular diagnosis of infective endocarditis by real-time broad-range polymerase chain reaction (PCR) and sequencing directly from heart valve tissue. *Medicine (Baltimore)* 2007; 86: 195–202.
118. Vandercam B, Jeumont S, Cornu O, *et al.* Amplification-based DNA analysis in the diagnosis of prosthetic joint infection. *J Mol Diagn* 2008; 10: 537–543.
119. Maskell NA, Batt S, Hedley EL, *et al.* The bacteriology of pleural infection by genetic and standard methods and its mortality significance. *Am J Respir Crit Care Med* 2006; 174: 817–823.
120. Jenkins C, Ling CL, Ciesielczuk HL, *et al.* Detection and identification of bacteria in clinical samples by 16S rRNA gene sequencing: comparison of two different approaches in clinical practice. *J Med Microbiol* 2012; 61: 483–488.
121. Hernes SS, Hagen E, Tofteland S, *et al.* Transthoracic fine-needle aspiration in the aetiological diagnosis of community-acquired pneumonia. *Clin Microbiol Infect* 2010; 16: 909–911.
122. Diederen BM, van Zwet AA, van der Zee A, *et al.* Community-acquired pneumonia caused by *Legionella longbeachae* in an immunocompetent patient. *Eur J Clin Microbiol Infect Dis* 2005; 24: 545–548.
123. Dorbecker C, Licht C, Korber F, *et al.* Community-acquired pneumonia due to *Bordetella holmesii* in a patient with frequently relapsing nephrotic syndrome. *J Infect* 2007; 54: e203–205.
124. Martinez MA, Ruiz M, Zunino E, *et al.* Detection of *Mycoplasma pneumoniae* in adult community-acquired pneumonia by PCR and serology. *J Med Microbiol* 2008; 57: 1491–1495.
125. Haider S, Collingro A, Walochnik J, *et al.* Chlamydia-like bacteria in respiratory samples of community-acquired pneumonia patients. *FEMS Microbiol Lett* 2008; 281: 198–202.
126. Keller PM, Rampini SK, Buchler AC, *et al.* Recognition of potentially novel human disease-associated pathogens by implementation of systematic 16S rRNA gene sequencing in the diagnostic laboratory. *J Clin Microbiol* 2010; 48: 3397–3402.
127. Kommedal O, Kvello K, Skjastad R, *et al.* Direct 16S rRNA gene sequencing from clinical specimens, with special focus on polybacterial samples and interpretation of mixed DNA chromatograms. *J Clin Microbiol* 2009; 47: 3562–3568.
128. Miyashita N, Fukano H, Mouri K, *et al.* Community-acquired pneumonia in Japan: a prospective ambulatory and hospitalised patient study. *J Med Microbiol* 2005; 54: 395–400.
129. Mosammaparast N, McAdam AJ, Nolte FS. Molecular testing for infectious diseases should be done in the clinical microbiology laboratory. *J Clin Microbiol* 2012; 50: 1836–1840.
130. Boudewijns M, Bakkers JM, Sturm PD, *et al.* 16S rRNA gene sequencing and the routine clinical microbiology laboratory: a perfect marriage? *J Clin Microbiol* 2006; 44: 3469–3470.
131. Fournier PE, Raoult D. Prospects for the future using genomics and proteomics in clinical microbiology. *Annu Rev Microbiol* 2011; 65: 169–188.
132. Hugenholtz P, Tyson GW. Microbiology: metagenomics. *Nature* 2008; 455: 481–483.

133. Cox MJ, Cookson WO, Moffatt MF. Sequencing the human microbiome in health and disease. *Hum Mol Genet* 2013; 22: R88–94.
134. Salipante SJ, Sengupta DJ, Rosenthal C, *et al.* Rapid 16S rRNA next-generation sequencing of polymicrobial clinical samples for diagnosis of complex bacterial infections. *PLoS One* 2013; 8: e65226.
135. Sundquist A, Bigdeli S, Jalili R, *et al.* Bacterial flora-typing with targeted, chip-based Pyrosequencing. *BMC Microbiol* 2007; 7: 108.
136. Gill SR, Pop M, Deboy RT, *et al.* Metagenomic analysis of the human distal gut microbiome. *Science* 2006; 312: 1355–1359.
137. Cabrera-Rubio R, Garcia-Nunez M, Seto L, *et al.* Microbiome diversity in the bronchial tracts of patients with chronic obstructive pulmonary disease. *J Clin Microbiol* 2012; 50: 3562–3568.
138. Conrad D, Haynes M, Salamon P, *et al.* Cystic fibrosis therapy: a community ecology perspective. *Am J Respir Cell Mol Biol* 2013; 48: 150–156.
139. Pallen MJ, Loman NJ, Penn CW. High-throughput sequencing and clinical microbiology: progress, opportunities and challenges. *Curr Opin Microbiol* 2010; 13: 625–631.
140. Armougom F, Bittar F, Stremler N, *et al.* Microbial diversity in the sputum of a cystic fibrosis patient studied with 16S rDNA pyrosequencing. *Eur J Clin Microbiol Infect Dis* 2009; 28: 1151–1154.

Chapter 4

The pathophysiology of pneumococcal pneumonia

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SUMMARY: Pneumococcal pneumonia is the explosive pulmonary and systemic inflammatory consequence of a disrupted host–pathogen relationship normally compartmentalised and optimally balanced as nasopharyngeal carriage. Pathogen, host and environmental factors combine to allow proliferation of pneumococci in the alveolar space. The local threat and the related threat of bacterial invasion resulting in sepsis are met with brisk responses from the epithelium and alveolar macrophages resulting in massive neutrophil ingress and loss of alveolar integrity. This immune response comes at the temporary cost of severely impaired respiratory function but, in most cases, is characterised by regulated resolution resulting in restoration of normal pulmonary architecture and function, as well as protection against future infection. The pathophysiology of pneumococcal pneumonia is informative in both treatment strategy and vaccine design. This chapter summarises recent discoveries in both host defence and pathogen virulence relating these subjects to future vaccination and treatment.

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Pneumonia caused by infection with *Streptococcus pneumoniae* is the most common and most studied bacterial cause of pneumonia [1], the pathogenesis of which has been recently reviewed [2]. Classical studies of human pathological specimens described severe (fatal) disease but, more recently, murine models have substantially advanced our understanding of the pathophysiology of infection [3]. More recently, human experimental infection studies [4] have confirmed many of the observations regarding colonisation and carriage first described in mice [5, 6]. The successful global implementation of effective vaccines to prevent pneumonia in childhood is underway but more work is needed in order to understand the means of improving survival in early, severe disease and, most importantly, the means to protect elderly people from this severe mucosal infection.

The relationship between pneumococcal carriage and pneumonia

Pneumococcal carriage

Pneumococcal carriage is the stable persistence of *S. pneumoniae* in the posterior nasopharynx [7]. It can be determined by swab or wash of the nasopharynx or oropharynx [8] and is mildly

symptomatic in children [9] but usually asymptomatic in adults. Pneumococcal carriage is of critical importance as the mode of community transmission of infection [10] and subsequent disease. Infants are colonised by pneumococci early in life and experience multiple episodes of carriage throughout their early years [11]. These episodes are immunising [12], resulting in both immunoglobulin and antigen-specific T-cell responses [13] at the respiratory mucosa and larynx [14, 15]. Host responses to both pneumococcal polysaccharide capsule and surface proteins are protective against further colonisation [16] and disease [17]. As a result of this developing immunity, the frequency and duration of pneumococcal carriage falls during early childhood [18] and this is accompanied by a fall in the incidence of pneumonia [19]. Pneumococcal conjugate vaccine in early life accelerates the development of this immunity and so reduces carriage, disease and transmission resulting in herd protection [20].

Colonisation and clearance of the nasopharynx

Pneumococci are almost uniquely found in humans and therefore reach the nasopharynx of an uncolonised host by inoculation of nasal secretions from a colonised person [7]. Pneumococci are highly resistant and remain infective by fomite spread even after 14 days of desiccation in the environment [21]. Transmission can be by aerosol but is more commonly by close contact including shared drink bottles [22], caring for children [23] or touching common objects such as door handles. The dose of inoculated pneumococci is not predictive of carriage in experimental human models [24]. Colonisation depends on binding of the pneumococcus to the host epithelium and evasion of host defence, particularly responses to pneumococcal polysaccharide capsule [25]. Pneumococcal protein virulence factors associated with binding include surface adhesins [26] (*e.g.* pneumococcal surface protein C (PspC) [27] and pneumococcal serine-rich protetin (PsrP) [28]) and factors that cause host cellular and matrix damage (*e.g.* pneumolysin and neuraminidase), but only the ability of the capsule to evade mucus layer defence correlates with observations of post-carriage protection in homologous human re-challenge [16]. Clearance of pneumococci from the nasopharynx is associated with antibody-dependent and antibody-independent mechanisms [29]. Eventual clearance of infection is associated with the development of an antigen-specific CD4 T-cell (T-helper cell (Th)17) response in mice [30, 31] and carriage is known to induce Th17 responses in the human lung [13].

Carriage as a risk for disease

Almost all episodes of carriage are benign and even beneficial as immunising events. Nevertheless, the anatomical continuity of the posterior nasopharynx with the trachea and lower airways makes lung contamination by the pneumococcus a near certainty and, therefore, pneumonia is an ever-present risk. Pneumococcal serotypes differ in their virulence [32] but, in general, aerosolised doses of bacteria can be cleared from the lung at much higher concentrations than those presented in droplets [33], suggesting that pneumonia may result from large numbers of pneumococci overwhelming alveolar defence. Clinical factors associated with increased aspiration, either by increased volume of nasal secretions or decreased laryngeal defence [34], are also associated with increased incidence of pneumonia. Pneumococcal pneumonia is common in young children [19] who have high rates of carriage and immature humoral and cellular defence, particularly an immature (splenic) B-cell response to capsular polysaccharide. Furthermore, pneumonia is particularly common in HIV-infected patients [35] who also have increased rates of pneumococcal carriage with a depleted CD4 repertoire [36] forming part of a defective humoral and cellular defence of the mucosal surface.

The epidemiology of pneumonia in elderly people is harder to explain [37]. Several published studies show that carriage rates in the elderly are very low [38]. Therefore, the very high incidence of pneumonia in this population [39] presents an interesting paradox. It has long been known, however, that recently acquired pneumococci pose a greater risk of disease than longer term commensals [11]. Recent data have shown that T-cell responses, particularly regulatory T-cells (Treg), are critical in maintaining the fine balance between pneumococcal carriage and disease [40];

this response is sub-optimal in HIV-infected adults [36] and may also be altered in the elderly [41]. It is probable that the low prevalence of carriage in older people is due to immune senescence and failure to contain pneumococci within the nasopharynx, which, in turn, is associated with rapid progression from acquisition to pneumonia.

Defence of the healthy lower respiratory tract

The incidence of pneumonia is remarkably low given the number of host encounters with potentially pathogenic bacteria. Most children tolerate multiple episodes of pneumococcal acquisition and carriage without a single episode of pneumonia. Moreover, this cannot simply be attributed to containment of bacteria within the nasopharynx as molecular techniques such as 16S ribosomal RNA gene sequencing show that even healthy lungs are host to a broad range of bacterial species [42]. Bacterial density is an important factor in the development of clinical pneumonia and the virulence phenotype of colonising pneumococci is actively altered through quorum sensing and the competence system to promote invasiveness when present in large numbers (see Competence system and biofilm section) [43].

The factors that enable pneumococci to reach dangerous numbers in a specific individual are rarely known but, given the significance of bacterial density, it is possible to understand why the lung has evolved a range of housekeeping strategies to restrict bacterial growth (fig. 1). The position of airway bifurcations and the mucociliary escalator reduce levels of particulate deposited in the lung. Lactoferrin secreted by the airway epithelium has direct bactericidal effects on the pneumococcus, and by sequestering iron, depletes the environment of this key bacterial nutrient; a strategy referred to as "nutritional immunity" [44]. Lysozyme is a highly effective anti-pneumococcal agent secreted from submucosal glands and present in high concentrations in the lower airway [45]. The human anti-microbial peptides (hAMPs) called human β-defensins (hBD1–hBD4) and the human cathelicidin-related antimicrobial peptide LL-37 [46] act synergistically with lysozyme and secreted phospholipases A2 to lyse bacteria, as well as limiting growth by restricting bacterial nutrient uptake [47–49]. Two collectins, surfactant proteins A and

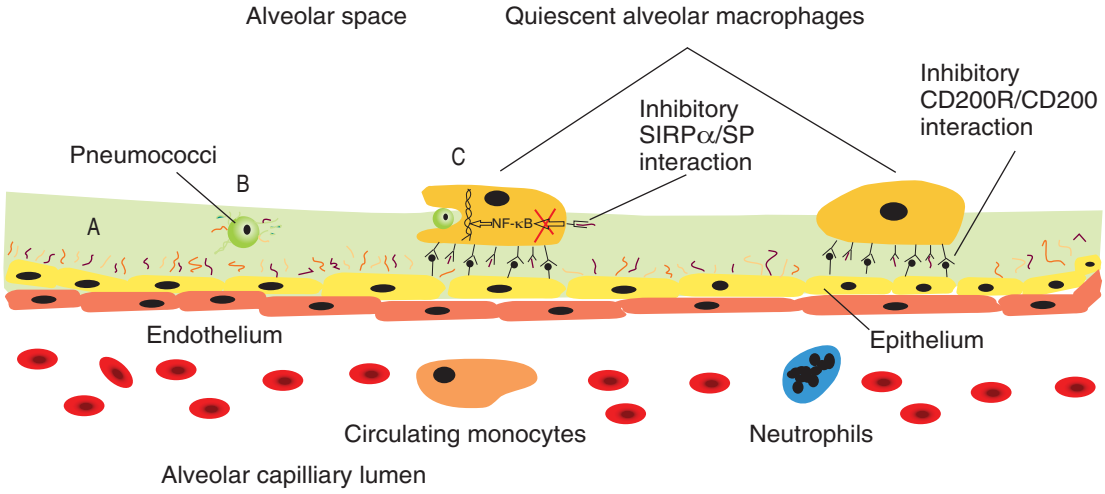

Figure 1. Key factors in the maintenance of lung immune homeostasis. A healthy alveolar epithelium is vital to the maintenance of innate immune homeostasis in the lung. A: Alveolar lining fluid is nutritionally barren and replete with antimicrobial compounds. B: Bacteria are lysed by secreted innate factors such as lysozyme, phospholipase-A2 and surfactant proteins (SP) A and D. C: Induction of an anti-inflammatory phenotype in alveolar macrophages. Phagocytic functions are maintained but the ability to present antigen and secrete pro-inflammatory cytokines is suppressed by surfactant proteins, granulocyte-macrophage colony-stimulating factor, interleukin-10 and transforming growth factor-β, and the CD200 and signal regulatory protein (SIRP)α interactions. NF-κB: nuclear factor-κB.

D (SP-A and SP-D, respectively), as well as being important opsonins, exert direct antimicrobial effects against pneumococci by altering cell permeability and by interfering with nutrient uptake [50, 51]. In homeostasis, resident alveolar macrophages can ingest the limited numbers of pneumococci that survive to reach the lung [52], but are actively suppressed to prevent disproportionate responses to innocuous stimuli.

The evolution of an acute pulmonary inflammatory response

The circumstances surrounding the switch from a homeostatic tolerance of low numbers of bacteria in the lower airway to an active immune response found in pneumonia and the signals, receptors and transducers of this response are the subject of intense study and some controversy [53, 54]. Classic macroscopic pathology describes the evolution of red hepatisation, grey hepatisation and resolution in pneumococcal pneumonia. These phases describe the collapse of endothelial integrity and ingress of large numbers of phagocytes with serum and some erythrocytes to the alveolar space, the gradual control of the infection and apoptosis of the cellular debris followed by resolution. These stages and their regulatory mechanisms have now been described in detail using murine models [55]. The complexity and sophistication of an aggressive immune response of the sort seen in pneumonia is impressive but it is important to remember that it frequently fails in the absence of antibiotics. In large parts of the world, antibiotic therapy availability is poor and mortality rates of 30–50% are similar to those recorded at the beginning of the 20th century [56].

The acute inflammatory stage

Bacteria can detect a favourable change in their environment and exploit this to multiply rapidly with potentially deleterious effects for the host; to match this, the host must respond rapidly. Most deaths from pneumococcal pneumonia occur soon after the onset of symptoms. This timeframe is too short for a naïve pneumococcal-specific adaptive immune response to contribute,

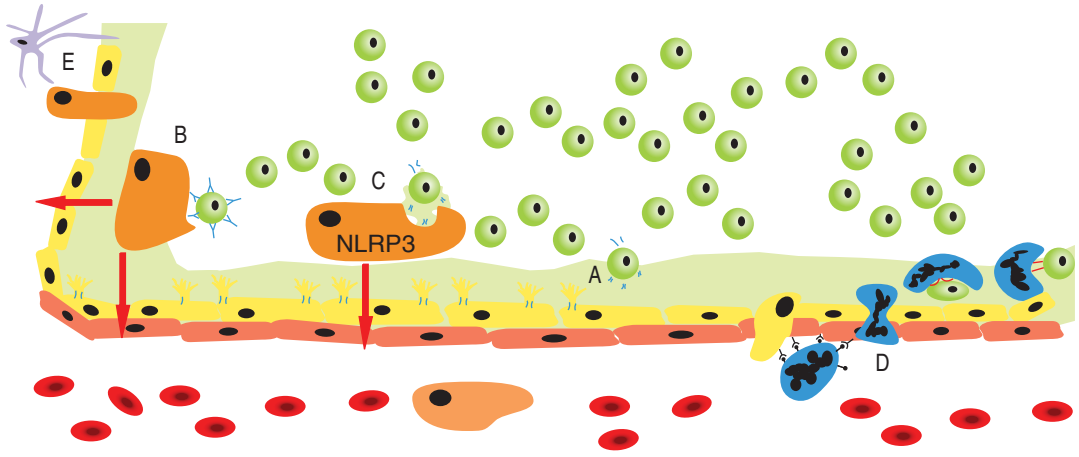

Figure 2. Escalation of the pneumonic immune response to pneumococcal threat**.** The clinical manifestation of pneumonia is the result of overwhelming numbers of pneumococci provoking an inflammatory response orchestrated by alveolar macrophages that have been unrestrained by a damaged, activated epithelium. A: Pneumolysin breaches the integrity of the cell walls releasing intracellular components, some of which are damage-associated molecular patterns. B: Macrophages recognise opsonised pneumococci and non-opsonised pneumococci *via* Toll-like receptor-2 and platelet activating factor receptor interactions with the pneumococcal cell wall constituents. C: Pneumolysin recognition leads to activation of the NLRP3 inflammasome. D: Activated neutrophils are recruited and translocate across the endothelium (integrin/intracellular adhesion molecule interaction) and epithelium (triggering receptor expressed on myeloid cells interaction (TREM)-1) into the alveolar lumen. E: Macrophages present antigen to dendritic cells and migrate to regional lymph nodes. The red arrows represent inflammatory cytokine and chemokine (*e.g.* CXCL8) release by activated macrophages and epithelium.

and the host must therefore rely on a rapid amplification of innate responses (fig. 2). The early response cells of the alveolus are the epithelium and the alveolar macrophage, which must sound an alarm of sufficient clarity to overcome the Treg [57] and alveolar macrophage [58] maintenance of normal quiescent lung homeostasis.

Recognition and signalling pathways

It is beyond the scope of this chapter to cover this complex area comprehensively but briefly, *S. pneumoniae* components can bind Toll-like receptors (TLRs) which span the cell wall of alveolar macrophages and epithelial cells [59]. Lipoteichoic acid is a constituent of the outer face of the cytoplasmic membrane of Gram-positive bacteria and is recognised by TLR2 but not TLR4 [60]. Certain DNA motifs from pneumococci can bind to TLR9 [61]. Several groups have demonstrated that key immune responses are only triggered by the simultaneous binding of host-derived products containing so-called damage-associated molecular patterns (DAMPS) along with pathogen-derived ligands called pathogen-associated molecular patterns (PAMPS) [62]. DAMPs include hyaluronic acid, host DNA and uric acid among others [63, 64]. This requirement for two signals may go some way to explaining why, in some circumstances, pneumococci can be recognised by TLRs without eliciting a pro-inflammatory response. TLRs expression on macrophages and epithelial cells can be upregulated during acute infection to facilitate better recognition of pathogen but, following influenza infection, TLR expression is significantly reduced rendering the lung susceptible to bacterial super infection [65].

Epithelium

The lung epithelium orchestrates the innate response to local damage, sets the threshold for this response, actively contributes to inhibiting excess bacterial growth, signals the escalation of an innate response, and escalates its own contribution to killing before returning the system to its homeostatic state [66]. The epithelium itself is highly plastic and many studies have shown that it can rapidly scale up its production of the antimicrobial effector molecules discussed previously. For example, changes in levels of SP-A and SP-D modulate the functions of antigen presenting cells such that the dynamics of neutrophil and T-cell recruitment are altered [51, 67]. Indeed several groups have shown that augmenting the innate immune response by stimulating the epithelium with microbial products allows a potentially lethal inoculum of pneumococci to be overcome [68]. When a more potent reaction is required, epithelial responses to intact pneumococci include production of soluble innate factors including CXCL8 [69] and upregulation of the platelet activating factor receptor (PAFr). The CXCL8 signal recruits neutrophils to the lung from the blood to tackle pneumococci but epithelial binding of pneumococcal cell wall phosphorylcholine by the PAFr [70] accelerates bacterial invasion. This example is typical of each phase of the host response to pneumococcus where a well-adapted host response has, in many cases, been abrogated by pathogen counter-evolution [71].

Alveolar macrophage

The alveolar macrophage has roles in pathogen detection, early alarm signalling and phagocytosis, followed by antigen presentation, neutrophil and lymphocyte recruitment, and coordination of the resolution of inflammation. Macrophage behaviour in the healthy alveolus is essentially anti-inflammatory. This is, in a large part, due to the inhibitory consequences of close physical interaction between alveolar macrophages and the airway epithelium. CD200 receptor (CD200R) on the macrophage surface binds the CD200 ligand on the surface of the epithelium [72]. Alveolar macrophages are induced to express very high levels of CD200R by high local levels of interleukin (IL)-10 and transforming growth factor-β, which are expressed on and secreted by the epithelium [73]. Another receptor expressed at high levels on alveolar macrophages is signal regulatory protein-α, which, *via* its interaction with SP-A and SP-D renders the cell quiescent [74]. Moreover, the uniquely high levels of granulocyte-macrophage colony-stimulating factor and SP-D to which alveolar macrophages are exposed lead to a dramatic reduction in their ability to present antigen in comparison with peritoneal counterparts [75]. Despite these restraints, macrophages can still recognise and phagocytose pneumococci but this does not result in an

escalation of inflammation whilst in their quiescent state. If bacterial density exceeds more than single numbers per macrophage, active phagocytosis is reduced and cytokine production increases. What is not clear is how macrophages become unbound by this suppression in the context of pneumonia. One possibility is that physical damage to the epithelium, for example due to lytic viruses such as influenza, leads macrophages to become detached from the CD200 interaction, releasing them from suppression [76]. In this context, the combined TLR signalling of pneumococcal PAMPs and DAMPs released from the lysed epithelium leads macrophages, released from the restraints imposed by the epithelium, to become activated. In the activated state, the phagocytosis of pneumococci leads to recognition by cytoplasmic nucleotide binding oligomerisation domain (NOD)-like receptors [77] and nuclear factor-κB transduced upregulation of multiple pro-inflammatory genes. The result of phagocytosis in this context is dramatic increases in the production of pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α, IL-1β, IL-6 and the neutrophil recruiting chemokine CXCL8 along with increased expression of a range of receptors for pathogen recognition [78]. Levels of pro-inflammatory cytokines seem to be similar when patients with pneumococcal pneumonia are compared to pneumonia caused by atypical pathogens, but the use of corticosteroids had little effect on cytokine levels in the context of pneumococcal pneumonia [79].

Neutrophils

The essential output of the epithelial and macrophage signalling pathways described earlier is the rapid recruitment of large numbers of these professional phagocytes. Neutrophils respond to CXCL8 by upregulating integrins [80] in order to bind endothelium and migrate into the alveolar space [81]. Neutrophils circulate in the pulmonary microvasculature at three times the concentration in peripheral venous blood owing to the stoichiometry of the phagocytes (stiff and large) compared with the microvasculature (narrow and compressed) [82]. This allows very rapid adhesion, migration and activation of neutrophils in response to local pulmonary epithelial signals [81].

The primary immune effector function in pneumococcal pneumonia is neutrophil-mediated phagocytosis. Phagocytosis of un-opsonised pneumococci occurs *via* a range of molecules including PAFr [83], SP-A, scavenger receptor-A [84] and MARCO (macrophage receptor with collagenous structure) [85]. However, these mechanisms of phagocytosis are inefficient compared to that of opsonised bacteria *via* Fc receptors, particularly FcγR (IgG receptor) and complement receptor binding. The complement system is vital to pneumococcal defence and, accordingly, many pneumococcal virulence factors, including PspC binding of factor H, have evolved specifically to subvert it. In addition to complement, other key opsonins include C-reactive protein, which binds teichoic acid and lipoteichoic acid of all *S. pneumoniae* serotypes and is secreted by epithelial cells in the lower airway [86]. SP-A and SP-D also bind opsonically to pneumococci and enhance neutrophil and macrophage uptake and killing [87, 88].

Adaptive immune response

In the heat of the inflammatory response, alveolar macrophages may transfer antigen to dendritic cells or migrate directly to the regional lymph node where cognate responses are developed with naïve T-cells to allow proliferation and production of appropriate IgG. This acquired response develops over weeks in naïve individuals but, owing to the immunological priming achieved by carriage exposures, boosted immune responses can normally occur within days of infection, resulting in high IgG levels in serum and exudative lung fluid. Dendritic cells play a key role at the interface between the innate and adaptive immune responses. Their phagocytosis of pneumococci leads to interactions with natural killer cells [89], pro-inflammatory cytokine release [62] and presentation of antigen to T-cells. Pneumococci subvert these functions by the potent inhibition of dendritic cell phagocytosis by pneumococcal adherence and virulence factor A (PavA) [90]. Moreover, the migration of dendritic cells from sites of infection to lymph nodes has recently been associated with deleterious effects and seems to facilitate pneumococcal dissemination [91].

Alveolar immunoglobulins (both IgG and IgA) to both pneumococcal capsule and pneumococcal proteins can be measured in most adults [92, 93]. Alveolar macrophages only exhibit full opsonophagocytic killing potential against pneumococcus in the presence of both cognate immunoglobulin and complement [94]. Antigen-specific T-cells responsive to pneumococcal antigens have been found in bronchoalveolar lavage from all healthy adults examined but their exact function is not known [24]. The Th17 subset has been shown to be increased by pneumococcal colonisation and is assumed to mediate pneumococcal killing by recruitment of neutrophils [13]. In the context of pneumococcal bacteraemia, marginal zone macrophages in the spleen that express SIGNR1 (specific intercellular adhesion molecule-grabbing non-integrin receptor 1) are vital for the initiation of IgM responses in early infection [95].

The control of infection and inflammation and resolution

Despite the innate and adaptive responses described above, if patients are untreated, the bacteria are not contained and at least 50% of patients die. The key to the de-escalation of the inflammatory response to the pneumococcus is the cessation of bacterial metabolism and replication, which is most successfully achieved using antibiotics. In the pre-antibiotic era, attempts were made to support patients by boosting their adaptive responses with serum therapy. Some patients responded but this approach was appropriately superseded by the widespread use of antibiotics [96].

Recent studies have described the importance of macrophage apoptosis in the evolution of an acute inflammatory response [52, 97]. Altered alveolar macrophage apoptosis results in impaired alveolar defence [97]. Pneumococci induce macrophage apoptosis by pneumolysin-dependent mechanisms (caspase dependent and caspase independent), but delayed apoptosis is required for evolution of the effective inflammatory response. As control is achieved over the invading bacterial population, macrophage phenotype changes again to support repair and macrophage apoptotic mechanisms allow the non-inflammatory resolution of some of the inflammatory exudates. Furthermore, effective neutrophil apoptosis pathways allow alveolar damage to be minimised even in the context of severe bacterial infection. At the height of the pneumonic illness, the alveolar space is clogged with serum, organised inflammatory debris, bacterial DNA and cellular debris. The process of macrophage efferocytosis (literally "burying the dead") allows restoration of normal pulmonary architecture and respiratory function [98]. To facilitate the return to homeostatic numbers, expanded populations of activated macrophages and dendritic cells in the pneumonic lung are depleted by the direct cytotoxic activity of γδT-cells [99].

Human susceptibility factors and association with disease and outcome

In humans, the striking epidemiological associations with disease are season, age, immunocompromise such as HIV, cigarette and biomass smoke exposure, and a range of comorbidities. Carriage frequency is closely related to age and HIV infection as discussed previously, but these factors, along with smoke exposure and immunocompromise, result in specific impairments of respiratory tract defence, particularly alveolar defence, resulting in susceptibility to pneumonia (table 1). CD4 depletion observed in HIV disease is associated with increases in IgG and IgA levels at the mucosal surface [125] but a loss of opsonophagocytic function [126] and antigen-specific CD4 cell loss [114].

Pneumonia is an illness-associated phenomenon and is one of the commonest causes of death in terminally ill patients [127]. It is closely associated with viral respiratory tract infection, in particular influenza and respiratory syncytial virus, and with chronic illnesses such as chronic obstructive pulmonary disease (COPD), cardiac failure, and renal or liver disease. The complex interaction of viral infection and pneumococcal pneumonia is covered in the chapter by RHODE [128] and will not be discussed here beyond the comment that influenza infection alters the

Table 1. Key associations of susceptibility to pneumococcal pneumonia

Risk factors	Mechanism	[Ref.]
Congenital factors		[100]
Complement deficiencies, *i.e.* components of the classical pathway	Impaired phagocytosis	[101, 102]
IRAK-4	Lack of response to TLR (not TLR3) or IL-1R agonists leads to impairment of IL-6 production and susceptibility to bacterial infection, in particular primary pneumococcal disease	[103]
NF-κB/IL-2 polymorphisms	Mechanism is unclear but may involve variations in CCL5 expression	[104]
MBL polymorphisms	The role of MBL deficiencies in pneumococcal pneumonia is controversial and recent studies suggest there may be no link	[105, 106]
FcγRIIA polymorphisms	These receptors are involved in neutrophil and macrophage phagocytosis but the direction of association between polymorphisms, susceptibility and outcome in pneumococcal disease is controversial	[100, 107]
PAD-PID	Leads to agammaglobulinaemia or, more commonly, hypogammaglobulinaemia and problems with class switching, resulting in frequent bacterial infections	[108]
Acquired factors		
Splenectomy and functional hyposplenism[#]	Impaired early production of natural antibodies by CD27 IgM memory B-cells and loss of splenic phagocytic capacity	[109, 110]
Cigarette smoke and biomass	Oxidative stress, impaired macrophage phagocytic function, impaired ciliary function and epithelial damage	[111–113]
HIV	Increased risk from early HIV infection due to multiple defects in innate and acquired immunity; risk increases substantially when CD4 count falls to <100	[114–116]
COPD	Pneumococci are associated with a substantial proportion of pneumonic and non-pneumonia exacerbations The epithelium is damaged and innate mechanisms are impaired Mucocilliary clearance, secretion of innate factors and macrophage TLR2 expression are reduced, and macrophage phagocytosis is impaired Use of inhaled steroids probably has a role	[117]
Asthma	Risk of pneumonia is increased Mechanisms are unclear but probably related to impairment of innate factors	[118]
ILD	In some series there is up to a 7-fold increase in rates of pneumococcal disease Mechanisms are unclear but probably related to impairment of epithelial function and innate factors	[119]
Cancer chemotherapy	Primary effect is neutropenia	[120]
Corticosteroids	May be related to impaired recruitment of neutrophils and pulmonary macrophages into the airway by inhibition of cytokine release, *e.g.* IL-6 and IL-8	[121]
Biological therapy for autoimmune disease	Anti TNF therapy increased the risk of pneumococcal pneumonia but specific mechanisms are unclear May be related to neutrophil recruitment	[122, 123]
Neurological disease	Mechanical factors lead to an increase in oropharyngeal contents and acute events (*e.g.* stroke) may have a direct immunosuppressive effect, including a reduction in CD4 T-cells and impaired T-cell function	[124]

IRAK-4: interleukin-1 receptor-associated kinase-4; NF-κB: nuclear factor-κB; IL: interleukin; MBL: mannose binding lectin; PAD: predominantly antibody defect; PID: primary immunodeficiencies; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; TLR: Toll-like receptor; IL-1R: interleukin-1 receptor; TNF: tumour necrosis factor. [#]: *e.g.* trauma, sickle cell disease, systemic lupus erythematosus, coeliac disease, alcoholism, *etc*.

epithelial surface to enhance bacterial binding [129] and lymphocyte cytokine production [130], and to decrease opsonophagocytic function for prolonged periods following severe infection [131]. The pathogenesis of COPD, asthma and interstitial lung diseases and their effects on airway defence have also been discussed elsewhere [119, 132]. However, emerging evidence suggests that diseases associated with increased rates of cell apoptosis, and consequently high rates of TAM-receptor mediated efferocytosis, may lead to exaggerated levels of macrophage suppression and susceptibility to bacterial infection [133]. Nutritional deficiency and liver disease also result in functional hypogammaglobulinaemia. Alcoholism is associated with increased susceptibility to pneumonia and this is, in part, related to immune dysfunction caused by alcohol [134]; specifically, patients with alcohol problems have impaired macrophage function and this in turn seems to be related to macrophage uptake of zinc [135].

Pneumococcal virulence factors

S. pneumoniae possesses a considerable armamentarium of virulence factors that it deploys in a co-ordinated fashion to enable its survival and propagation within multiple niches in its human host (table 2). The most important attributes of a successful virulence phenotype are: 1) adherence to and translocation through epithelial surfaces; 2) direct toxin-mediated tissue damage; 3) subversion of host immune responses, particularly complement-mediated opsonophagocytosis; 4) resistance to conditions of oxidative stress and nutrient deficiency; and 5) quorum sensing and bacterial competence [3]. Whilst many virulence factors have been recognised for several decades, the ability to precisely manipulate pneumococcal genotype using signature-tagged mutagenesis (STM) has greatly expanded the repertoire of recognised virulence factors. Comparative genomic analysis (CGA) and the use of capsule-switched mutants have revealed the importance of interactions between virulence factors in determining the overall pathogen phenotype. It is, however, important to appreciate that the clinical significance of many putative virulence factors identified in murine models of infection has not been categorically demonstrated. It is notable that the relevance of some putative virulence factors identified using STM in murine models has not been corroborated in CGA of clinical isolates [166]. This distinction may prove prescient as the therapeutic applications of protein virulence factors (*e.g.* vaccine candidates and targets for immunomodulatory therapy) are explored.

Genetics of pneumococcal virulence

Individual isolates of *S. pneumoniae* vary markedly in their propensity to cause invasive disease. Although the characteristics of the polysaccharide capsule go some way to explaining this variation, clear differences in invasiveness amongst isolates of the same serotype are well described [167]. Even amongst isolates of the same clonal lineage, defined by multi-locus sequencing type (MLST), there are important differences in virulence phenotype [168]. Recent evidence suggests that subtle but important genetic differences between pneumococcal isolates reflect stable adaptations to specific selective pressures present within particular environmental niches in the human host. When used in a murine nasal challenge model, clinical pneumococcal isolates of the same serotype and similar MLST display marked variation in virulence phenotype depending on the *in vivo* site of isolation [169]. Clinical blood isolates caused bacteraemia without first establishing colonisation, whilst isolates from ear infections colonised the nasopharynx and spread to the ear, but did not cause invasive disease.

CGA of clinical pneumococci has demonstrated that individual isolates possess a core genome that is common to all strains and a variable set of additional genes that correlate closely with virulence phenotype [166, 170]. The core genome, as well as encoding housekeeping functions, includes many major virulence factors (*e.g.* hyaluronate lyase (HylA) and pyruvate oxidase (SpxB)), which may indicate that, whilst necessary, these genes alone are not sufficient to determine the propensity of an isolate to cause invasive disease [170]. Many of the variable genes cluster in accessory regions, in keeping with the known propensity of pneumococci to

acquire genetic material by horizontal passage from co-colonising bacteria. The pattern of accessory regions present in invasive isolates varies with serotype [166, 170]. It is plausible that, given the dominant effect of the polysaccharide capsule on pneumococcal biology, the complement of additional virulence factors required to produce an effective virulence phenotype varies [171].

Pneumococcal transcriptomics and tissue specificity of virulence factors

The dynamic nature of virulence factor expression during the progression of pneumococcal infection has been demonstrated with increasing levels of sophistication in recent years. In an elegant series of experiments, ORIHUELA *et al.* [172] demonstrated that not only were particular virulence factors involved in tissue-specific replication, but distinct factors were required to allow transition between body sites. For example, pneumolysin was required for replication in the lungs and both translocation to and survival in the bloodstream. PspC (also referred to as CbpA or choline binding protein A) contributed to both transition from upper to lower respiratory tracts and from blood to cerebrospinal fluid, but was redundant for tissue replication. Similarly, the novel bacterial adhesion PsrP is required for bacterial invasion from the lungs, but not for nasopharyngeal colonisation or survival in the bloodstream [28, 170].

Emerging transcriptomic data give a more complete and nuanced picture of the coordinated expression of virulence determinants. Two main patterns of *in vivo* gene expression by *S. pneumoniae* have been described: the first relating to bacteria in the bloodstream characterised by increased expression of pneumolysin and PspA; and the second of bacteria isolated from tissues (*i.e.* lungs and brain) showing increased expression of neuraminidases, metalloproteinases, and oxidative stress and competence genes [43]. More recently, OGUNNIYI *et al.* [173] described differences in the transcriptomic profile between pneumococci obtained from nasopharynx, lung and blood following intranasal infection. The relevance of selected differentially expressed genes was confirmed by targeted mutagenesis, which rendered organisms completely avirulent or significantly attenuated for virulence in a specific host niche. For example, the ATP binding cassette-iron transporter component, pneumococcal iron uptake A (PiuA), was among the genes upregulated in the blood and Δ*piuA* mutants were avirulent. Furthermore, immunisation with recombinant PiuA was protective against sepsis [173].

Polysaccharide capsule

The extracellular polysaccharide capsule of *S. pneumoniae* potently inhibits phagocytosis and is essential for the organism's virulence [174]. The 93 antigenically distinct capsular serotypes differ markedly in their potential to cause invasive disease in proportion with their relative resistance to phagocytosis [136]. Furthermore, capsular serotype is an independent determinant of outcome of invasive pneumococcal disease [175].

In the absence of capsule-specific antibodies, opsonophagocytosis of *S. pneumoniae* is predominantly complement mediated. The polysaccharide capsule inhibits both the classical and alternative pathways through distinct mechanisms, limiting the deposition of the C3b/iC3b on the bacterial surface [136, 137]. The highly negatively charged capsule also sterically inhibits the interaction between deposited C3b and complement receptors [176].

Whilst the importance of the capsule for systemic virulence is clear, its role in early infection is more complicated. The capsule promotes transit of pneumococci to the nasopharyngeal epithelial surface by inhibiting mucous binding [25]. However, once at the epithelial surface, organisms expressing thin capsules (transparent phase) preferentially establish stable colonisation [177]. Following invasion, survival is favoured by increased capsular expression (opaque phase), conferring resistance to opsonophagocytosis. The mechanisms whereby pneumococci alter the

Table 2. Pneumococcal virulence factors grouped according to main function in pneumonia

Virulence factor	Main function in pneumococcal disease	[Ref.]
Resistance to opsonophagocytosis		
Polysaccharide capsule	Resistance to opsonophagocytosis by inhibition of classical and alternative complement pathways; reduces trapping by NETs; inhibits mucus binding promoting transit to epithelial surface	[3, 136–138]
PspA	Limits C3b deposition by blocking formation of alternative pathway C3 convertase; inhibits bactericidal actions of apolactoferrin	[139–141]
PspC[#]	Limits C3b formation by binding factor H; initiates invasion through binding human polymeric immunoglobulin receptor	[27, 142]
IgA protease	Cleaves IgA-surface bound Fab fragments limiting opsonophagocytosis and exposing phosphorylcholine that promotes adherence by binding PAFr	[3]
PhtA, B, D and E	Reduction of complement deposition *via* factor H recruitment	[143]
EndA	Degradation of DNA in NETs favouring subsequent invasion	[144]
Degradation of ECM		
NanA	Removes terminal sialic acid residues from cell surface glycopeptides promoting adherence; confers resistance to complement deposition	[145, 146]
BgaA and StrH	Expose glycopeptides for pneumococcal epithelial binding; reduce C3b deposition	[147]
Hyl	Degrades hyaluronan in the ECM facilitating bacterial spread and tissue invasion	[148]
Enolase	Binds plasminogen promoting transmigration through ECM; contributes to complement evasion by binding complement inhibitor C4b-binding protein	[149, 150]
SpuA	Glycogen degradation enzyme required for full virulence; mechanism of action uncertain	[151]
Epithelial adhesion		
Pili	Promotes epithelial adherence and tissue invasion; associated with resistance to intracellular killing within macrophages	[152, 153]
PsrP	Adhesin required for bacterial persistence in lungs	[28]
SrtA	Anchors cell surface proteins, promoting bacterial epithelial adherence	[154]
PavA	Binds fibronectin facilitating stable colonisation	[155, 156]
PavB	Binds fibronectin and plasminogen; promotes colonisation and lung transmigration	[157]
PcpA	Surface protein induced by low-manganese concentrations that contributes to epithelial adherence	[158]
Tissue damage and pro-inflammatory response		
Pneumolysin	Cytolysis; complement activation; induction of host inflammatory response *via* multiple pathways; inhibition of phagocyte respiratory burst and ciliary beating on epithelium	[55, 62, 159]
LytA	Induces autolysis by peptidoglycan cleavage, and release of pneumolysin and inflammatory cell wall components (*e.g.* teichoic acids)	[148]
Phosphorlycholine	Binds PAFr on nasopharyngeal epithelial cells and activates host cell signalling pathways	[3]
Lipoteichoic acid	Induces proinflammatory response, platelet and coagulation pathway activation *via* TLR2 and probably TLR4 and PAFr binding	[160]
Resistance to nutrient deficiency and oxidative stress		
PsaA	Mediates divalent metal-ion uptake, required for resistance to oxidative stress, and regulates expression of bacterial adhesins	[3]
PiaA and PiuA	Lipoprotein components of ABC transporters that acquire iron for bacterial growth	[161]
SodA	Confers protection against extracellular oxidative stress	[162]

Table 2. Continued

Virulence factor	Main function in pneumococcal disease	[Ref.]
ClpP	Confers resistance to oxidative stress following macrophage phagocytosis	[163]
Bacterial competition and co-operation		
Biofilm and competence	Differential regulation of virulence factors by CSP in bacteraemia and pneumonia; production correlates with expression of biofilm	[2, 43]
Bacteriocin	Mediates intraspecies competition between co-colonising pneumococcal strains in the nasopharynx	[164]
SpxB	Inhibits co-colonising bacteria *via* hydrogen peroxide production	[165]

PspA: pneumococcal surface protein A; PspC: pneumococcal surface protein C; Pht: polyhistidine triad; EndA: endonuclease A; ECM: extracellular matrix; NanA: neuraminidase; BgaA: β-galactosidase; StrH: β-*N*-acetylglucosaminidase; Hyl: hyaluronate lyase; SpuA: pullulanase; PsrP: pneumococcal serine-rich protein; SrtA: sortase A; PavA: pneumococcal adhesion and virulence A; PavB: pneumococcal adhesion and virulence B; PcpA: pneumococcal choline binding protein A; LytA: autolysin; PsaA: pneumococcal surface antigen A; PiaA: pneumococcal iron acquisition A; PiuA: pneumococcal iron uptake A; SodA: manganese superoxide dismutase; ClpP: ATP-dependent caseinolytic protease; SpxB: pyruvate oxidase; NET: neutrophil extracellular trap; PAFr: platelet activating factor receptor; TLR: Toll-like receptor; ABC: ATP-binding cassette; CSP: competence stimulating peptide. #: also known as choline binding protein A.

degree of expression of the capsule to adapt to particular host niches are yet to be fully elucidated, but may relate to changes in oxygen tension [178].

Pneumolysin

Pneumolysin is a highly conserved toxin that is central to both pneumococcal virulence and the induction of the host inflammatory response. Upon release from the bacterial cytoplasm, which is predominantly mediated by LytA-induced autolysis, pneumolysin monomers combine to form transmembrane pores that induce direct host tissue damage and facilitate bacterial invasion [176]. The pulmonary inflammatory response to pneumolysin is characterised by the release of proinflammatory cytokines and chemokines and the sequential recruitment of neutrophils and activated T- and B-lymphocytes [55]. The signalling pathways mediating the response to pneumolysin are complex. Previous studies have suggested a role for TLR4 [179] and TLR2 [180], but recent data show that pneumolysin can induce the production of pro-inflammatory cytokines independently of TLR4, *via* NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome [62]. *In vitro*, pneumolysin acts synergistically to enhance the secretion of pro-inflammatory cytokines in response to TLR agonists. It is plausible that pneumolysin could potentiate TLR-mediated inflammatory responses to other pneumococcal components and endogenous products released during pneumococcal infection [62].

The interaction of the cytolytic and immune-activating features of pneumolysin has an important bearing on the outcome of pneumococcal infection. Only pneumococci expressing pneumolysin with haemolytic activity induce a protective host response *via* the NLRP3 inflammasome pathway [62, 181]. Pneumococci expressing pneumolysin with markedly reduced cytolytic activity appear to have an early growth advantage in blood [182] and, moreover, have been identified in disease outbreaks in humans, including invasive pneumococcal disease [183]. It is plausible that the robust innate response induced by cytolytic toxins more effectively holds in check early bacterial replication.

Pneumolysin represents both a candidate protein for a serotype-independent vaccine and a target for adjunctive therapy. Immunisation with the pneumolysin variant PdB showed protective efficacy in pneumonia [184] and sepsis [185], but residual cytolytic activity may hamper clinical development [186]. The PlyD1 variant holds considerable promise. In murine models, immunisation was protective against pneumococcal infection and recently reported phase I studies indicate that it is both immunogenic and well-tolerated [187]. Curtailing the inflammatory effects of pneumolysin is a potential strategy to improve pneumonia outcomes. Some of the

apparent additive benefit of combination treatment with macrolides in pneumococcal pneumonia may be attributable to reduction in pneumolysin production [188].

Pneumococcal surface protein A

PspA is an important virulence determinant in murine models of pneumococcal infection and probably also in humans since it is universally expressed in clinical pneumococcal isolates [139]. It inhibits the bactericidal activity of the secreted innate immune protein apolactoferrin [139] and reduces complement-dependent phagocytosis by inhibiting the formation and/or function of the alternative pathway C3 convertase [140].

PspA holds considerable promise as a protein vaccine candidate. Immunisation using recombinant protein elicits protection against pneumonia, sepsis and nasopharyngeal colonisation in mice [139]. Moreover, passive transfer of human antibodies raised against recombinant PspA is also protective [189]. A wide range of PspA-based immunisation strategies are currently in various stages of clinical development.

Pilus proteins

The presence of a pilus in some pneumococcal strains has only been recognised recently [190]. This long structural organelle projects from the cell wall, protrudes through the capsule and promotes adherence to the respiratory epithelium. Isolates with pili out-compete non-piliated rivals to establish nasopharyngeal colonisation and have enhanced virulence in models of pneumonia and bacteraemia [190]. The pilus is encoded by the *rlrA* pathogenicity islet (accessory region), which comprises of genes for three structural proteins RrgA, RrgB and RrgC, and three associated sortases [191]. The RrgA component is the main determinant of adhesion [152] and also invokes a host inflammatory response *via* TLR2 [192]. RrgA is also implicated in the systemic invasion of pneumococci; pneumococci expressing RrgA are preferentially phagocytosed by macrophages and show prolonged intracellular survival and higher rates of early bacteraemia [153]. Immunisation with recombinant pilus subunits confers protection against lethal pneumococcal challenge in mice [193]. However, the relevance of pilus in human pneumococcal disease and its potential use as a vaccine candidate is unclear since it is expressed by as few as 21% of invasive clinical isolates [194].

Competence system and biofilm

A particular trait of streptococci is their inclination to undergo natural genetic transformation facilitating the efficient selection of alleles most suited to the local environment [195]. In the pneumococcus, the ability or ''competence'' for genetic transformation is a dynamic phenotype that is closely controlled by a quorum sensing system known as COM [195]. The switch from non-competence to competence is regulated by quorum sensing the levels of a substance called competence stimulating peptide (CSP) in the surrounding milieu [196]. Levels of CSP are directly related to the density of pneumococci in an area; once a threshold level of CSP is reached, the pneumococci can switch to the competent state if the environmental conditions are suitable.

Manipulation of the COM system modulates pneumococcal virulence in a tissue-specific manner; CSP increases virulence in pneumonia and meningitis, but reduces it in bacteraemic sepsis [43]. *In vitro* culture, CSP induces bacterial growth in biofilm. It is plausible that biofilm formation confers a survival advantage during tissue infections such as pneumonia, but is irrelevant or even deleterious in bacteraemia when planktonic growth is favoured. In addition to transcriptional regulation of growth pattern during the course of infection, recent evidence indicates stable genotypic adaptation of pneumococci to particular host niches. The growth pattern *in vitro* of clinical pneumococcal isolates differs markedly according to the site of isolation. Blood and ear infection isolates required media composition that resembled their respective site of isolation for optimal *in vitro* growth [169].

Therapeutic possibilities for vaccination and treatment

Potential vaccination strategies

Adults rarely suffer pneumonia from recurrent episodes of the same infecting pneumococcal serotype and yet the pneumococcal polysaccharide vaccine does not offer protective immunity against pneumonia in elderly people or prevent carriage in adults. The reasons for this paradox are not fully understood but are related to compartmental differences in systemic and mucosal immunity [197]. The polysaccharide vaccine does give effective protection against invasive pneumococcal disease and this is associated with increased serum anti-capsular IgG. However, despite increasing serotype-specific IgA levels in the lungs of vaccinated patients [198], polysaccharide vaccination leads to a persistent depletion of capsule specific B-cells that may explain an increase in mucosal disease [199]. It is reasonable to assume that the inflammatory response to pneumonia elicits both systemic and mucosal cellular immune responses to capsule, protein and conjugated capsular antigens. An effective vaccine against pneumonia will have to elicit these responses and current research is focused on the antigens (see previous section), route of administration and adjuvant that will be needed to make this a reality.

Potential novel treatments

Strategies to improve outcomes of severe pneumococcal pneumonia are urgently needed. Despite the use of effective antimicrobial agents that rapidly clear pneumococci from both the lungs and bloodstream, early mortality remains high. The deleterious effects of a dysregulated and over-exuberant systemic inflammatory response may contribute to early mortality [200]; adjunctive treatments that limit or modulate the host response remain the focus of considerable interest but their effectiveness in improving outcome is as yet unproven. For example, the use of corticosteroids in pneumonia has been repeatedly examined over the last 50 years with varying results, but no consistent evidence of benefit has been demonstrated [201]. Both macrolides and statins exert pleiotropic immunomodulatory effects that may be useful in the treatment of pneumococcal pneumonia and some observational data support their use, but evidence from prospective randomised trials is currently lacking [202, 203].

Other therapeutic approaches in development aim to target key components of the host response more precisely. TNF-related apoptosis-inducing ligand (TRAIL) induces apoptosis in both alveolar macrophages and neutrophils, a process which is central to the resolution of pulmonary inflammatory responses to pneumococcal infection [52, 100]. TRAIL-deficient mice show impaired bacterial clearance, excessive lung inflammatory responses, and reduced survival during pneumococcal pneumonia. Administration of TRAIL, however, dramatically improved survival [204].

Another promising novel therapeutic approach for pneumococcal pneumonia focuses on augmenting pulmonary pathogen clearance. The immune activating peptide P4, which incidentally is a surface expressed moiety of the pneumococcal surface antigen A (PsaA), augments the response to passive immunotherapy by enhancing the ability of neutrophils and macrophages to phagocytose opsonised pneumococci [205]. Intranasal P4 in combination with intravenous immunoglobulin rescued mice from fatal pulmonary pneunomococal challenge and prevented the onset of bacteraemia and sepsis even without antibiotic treatment [205]. A similar biological action of P4 using *ex vivo* human alveolar macrophages has been demonstrated and clinical studies are now planned [206].

Conclusion

Pneumococcal pneumonia is an infrequent but severe consequence of frequent bacterial exposure. Immune defence is usually effective at containing carriage but struggles in the face of full blown

infection. Modern scientific methods have generated information likely to lead to new vaccines and treatments.

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Statement of Interest

None declared.

References

1. White B, Robinson ES, Barnes LA, eds. The Biology of Pneumococcus. The Bacteriological, Biochemical, and Immunological Characters and Activities of *Diplococcus pneumoniae*. New York, The Commonwealth Fund, 1938.
2. van der Poll T, Opal SM. Pathogenesis, treatment, and prevention of pneumococcal pneumonia. *Lancet* 2009; 374: 1543–1556.
3. Kadioglu A, Weiser JN, Paton JC, *et al.* The role of *Streptococcus pneumoniae* virulence factors in host respiratory colonization and disease. *Nat Rev Microbiol* 2008; 6: 288–301.
4. Gritzfeld JF, Wright AD, Collins AM, *et al.* Experimental human pneumococcal carriage. *J Vis Exp* 2013; 15: pi, 50115.
5. Wu HY, Virolainen A, Mathews B, *et al.* Establishment of a *Streptococcus pneumoniae* nasopharyngeal colonization model in adult mice. *Microb Pathog* 1997; 23: 127–137.
6. Ogunniyi AD, LeMessurier KS, Graham RMA, *et al.* Contributions of pneumolysin, pneumococcal surface protein A (PspA), and PspC to pathogenicity of *Streptococcus pneumoniae* D39 in a mouse model. *Infect Immun* 2007; 75: 1843–1851.
7. Bogaert D, de Groot R, Hermans PW. *Streptococcus pneumoniae* colonisation: the key to pneumococcal disease. *Lancet Infect Dis* 2004; 4: 144–154.
8. van Dongen TM, van der Heijden GJ, van Zon A, *et al.* Evaluation of concordance between the microorganisms detected in the nasopharynx and middle ear of children with otitis media. *Pediatr Infect Dis J* 2013; 32: 549–552.
9. Rodrigues F, Foster D, Nicoli E, *et al.* Relationships between rhinitis symptoms, respiratory viral infections and nasopharyngeal colonization with *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus* in children attending daycare. *Pediatr Infect Dis J* 2013; 32: 227–232.
10. Simell B, Auranen K, Kayhty H, *et al.* The fundamental link between pneumococcal carriage and disease. *Expert Rev Vaccines* 2012; 11: 841–855.
11. Gray BM, Converse GM, Dillon HC. Epidemiologic studies of *Streptococcus pneumoniae* in infants: acquisition, carriage, and infection during the first 24 months of life. *J Infect Dis* 1980; 142: 923–933.
12. Rapola S, Jäntti V, Haikala R, *et al.* Natural development of antibodies to pneumococcal surface protein A, pneumococcal surface adhesin A, and pneumolysin in relation to pneumococcal carriage and acute otitis media. *J Infect Dis* 2000; 182: 1146–1152.
13. Wright AKA, Bangert M, Gritzfeld JF, *et al.* Experimental human pneumococcal carriage augments IL-17A-dependent T-cell defence of the lung. *PLoS Pathog* 2013; 9: 1–12.
14. Zhang Q, Leong SC, McNamara PS, *et al.* Characterisation of regulatory T cells in nasal associated lymphoid tissue in children: relationships with pneumococcal colonization. *PLoS Pathog* 2011; 7: e1002175.
15. Pido-Lopez J, Kwok WW, Mitchell TJ, *et al.* Acquisition of pneumococci specific effector and regulatory $CD4^+$ T cells localising within human upper respiratory-tract mucosal lymphoid tissue. *PLoS Pathog* 2011; 7: e1002396.
16. Ferreira DM, Neill DR, Bangert M, *et al.* Controlled human infection and rechallenge with *Streptococcus pneumoniae* reveals the protective efficacy of carriage in healthy adults. *Am J Respir Crit Care Med* 2013; 187: 855–864.
17. Barocchi MA, Censini S, Rappuoli R. Vaccines in the era of genomics: the pneumococcal challenge. *Vaccine* 2007; 25: 2963–2973.
18. Weinberger DM, Dagan R, Givon-Lavi N, *et al.* Epidemiologic evidence for serotype-specific acquired immunity to pneumococcal carriage. *J Infect Dis* 2008; 197: 1511–1518.
19. O'Brien KL, Wolfson LJ, Watt JP, *et al.* Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet* 2009; 374: 893–902.

20. Whitney CG, Pilishvili T, Jackson D, *et al.* Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med* 2003; 348: 1737–1746.
21. Walsh RL, Camilli A. *Streptococcus pneumoniae* is desiccation tolerant and infectious upon rehydration. *MBio* 2011; 2: e00092–11.
22. Levine H, Balicer RD, Zarka S, *et al.* Dynamics of pneumococcal acquisition and carriage in young adults during training in confined settings in Israel. *PLoS One* 2012; 7: e46491.
23. Givon-Lavi N, Fraser D, Porat N, *et al.* Spread of *Streptococcus pneumoniae* and antibiotic-resistant *S. pneumoniae* from day-care center attendees to their younger siblings. *J Infect Dis* 2002; 186: 1608–1614.
24. Wright AKA, Ferreira DM, Gritzfeld JF, *et al.* Human nasal challenge with *Streptococcus pneumoniae* is immunising in the absence of carriage. *PLoS Pathog* 2012; 8: e1002622.
25. Nelson AL, Roche AM, Gould JM, *et al.* Capsule enhances pneumococcal colonization by limiting mucus-mediated clearance. *Infect Immun* 2007; 75: 83–90.
26. Hammerschmidt S. Adherence molecules of pathogenic pneumococci. *Curr Opin Microbiol* 2006; 9: 12–20.
27. Zhang JR, Mostov KE, Lamm ME, *et al.* The polymeric immunoglobulin receptor translocates pneumococci across human nasopharyngeal epithelial cells. *Cell* 2000; 102: 827–837.
28. Rose L, Shivshankar P, Hinojosa E, *et al.* Antibodies against PsrP, a novel *Streptococcus pneumoniae* adhesin, block adhesion and protect mice against pneumococcal challenge. *J Infect Dis* 2008; 198: 375–383.
29. Li Y, Gierahn T, Thompson CM, *et al.* Distinct effects on diversifying selection by two mechanisms of immunity against *Streptococcus pneumoniae. PLoS Pathog* 2012; 8: e1002989.
30. Zhang Z, Clarke TB, Weiser JN. Cellular effectors mediating Th17-dependent clearance of pneumococcal colonization in mice. *J Clin Invest* 2009; 119: 1899–1909.
31. Lu YJ, Gross J, Bogaert D, *et al.* Interleukin-17A mediates acquired immunity to pneumococcal colonization. *PLoS Pathogens* 2008; 4: e1000159.
32. Mohler J, Azoulay-Dupuis E, Amory-Rivier C, *et al. Streptococcus pneumoniae* strain-dependent lung inflammatory responses in a murine model of pneumococcal pneumonia. *Intensive Care Med* 2003; 29: 808–816.
33. Yershov AL, Jordan BS, Guymon CH, *et al.* Relationship between the inoculum dose of *Streptococcus pneumoniae* and pneumonia onset in a rabbit model. *Eur Respir J* 2005; 25: 693–700.
34. Cabre M. Pneumonia in the elderly. *Curr Opin Pulm Med* 2009; 15: 223–229.
35. Janoff EN, Breiman RF, Daley CL, *et al.* Pneumococcal disease during HIV infection. Epidemiologic, clinical, and immunologic perspectives. *Ann Intern Med* 1992; 117: 314–324.
36. Glennie SJ, Banda D, Gould K, *et al.* Defective pneumococcal-specific Th1 responses in HIV-infected adults precedes a loss of control of pneumococcal colonization. *Clin Infect Dis* 2013; 56: 291–299.
37. Meyer KC. The role of immunity and inflammation in lung senescence and susceptibility to infection in the elderly. *Semin Respir Crit Care Med* 2010; 31: 561–574.
38. Ridda I, Macintyre CR, Lindley R, *et al.* Lack of pneumococcal carriage in the hospitalised elderly. *Vaccine* 2010; 28: 3902–3904.
39. Welte T, Kohnlein T. Global and local epidemiology of community-acquired pneumonia: the experience of the CAPNETZ Network. *Semin Respir Crit Care Med* 2009; 30: 127–135.
40. Neill DR, Fernandes VE, Wisby L, *et al.* T regulatory cells control susceptibility to invasive pneumococcal pneumonia in mice. *PLoS Pathog* 2012; 8: e1002660.
41. Raynor J, Lages CS, Shehata H, *et al.* Homeostasis and function of regulatory T cells in aging. *Curr Opin Immunol* 2012; 24: 482–487.
42. Charlson ES, Bittinger K, Bushman FD, *et al.* Topographical continuity of bacterial populations in the healthy human respiratory tract. *Am J Respir Crit Care Med* 2011; 184: 957–963.
43. Oggioni MR, Trappetti C, Kadioglu A, *et al.* Switch from planktonic to sessile life: a major event in pneumococcal pathogenesis. *Mol Microbiol* 2006; 61: 1196–1210.
44. Arnold RR, Brewer M, Gauthier JJ. Bactericidal activity of human lactoferrin: sensitivity of a variety of microorganisms. *Infect Immun* 1980; 28: 893–898.
45. Dajani R, Zhang YL, Taft PJ, *et al.* Lysozyme secretion by submucosal glands protects the airway from bacterial infection. *Am J Physiol Lung Cell Mol Biol* 2005; 32: 548–552.
46. Cruse G, Fernandes VE, De Salort J, *et al.* Human lung mast cells mediate pneumococcal cell death in response to activation by pneumolysin. *J Immunol* 2010; 184: 7108–7115.
47. Masuda S, Murakami M, Mitsuishi M, *et al.* Expression of secretory phospholipase A2 enzymes in lungs of humans with pneumonia and their potential prostaglandin-synthetic function in human lung-derived cells. *Biochem J* 2005; 387: 27–38.
48. Tecle T, Tripathi S, Hartshorn KL. Defensins and cathelicidins in lung immunity. *Innate Immunity* 2010; 16: 151–159.
49. Zhao H, Kinnunen PKJ. Modulation of the activity of secretory phospholipase A2 by antimicrobial peptides. *Antimicrob Agents Chemother* 2003; 47: 965.
50. Haczku A. Protective role of the lung collectins surfactant protein A and surfactant protein D in airway inflammation. *J Allergy Clin Immunol* 2008; 122: 861–879.
51. Jounblat R, Clark H, Eggleton P, *et al.* The role of surfactant protein D in the colonisation of the respiratory tract and onset of bacteraemia during pneumococcal pneumonia. *Respir Res* 2005; 6: 126–126.

52. Dockrell DH, Marriott HM, Prince LR, *et al.* Alveolar macrophage apoptosis contributes to pneumococcal clearance in a resolving model of pulmonary infection. *J Immunol* 2003; 171: 5380–5388.
53. Pradeu T, Cooper EL. The danger theory: 20 years later. *Front Immunol* 2012; 3: 287.
54. Eberl G. A new vision of immunity: homeostasis of the superorganism. *Mucosal Immunol* 2010; 3: 450–460.
55. Kadioglu A, Gingles NA, Grattan K, *et al.* Host cellular immune response to pneumococcal lung infection in mice. *Infect Immun* 2000; 68: 492–501.
56. Mulholland K. Perspectives on the burden of pneumonia in children. *Vaccine* 25: 2394–2397.
57. Belkaid Y. Regulatory T cells and infection: a dangerous necessity. *Nat Rev Immunol* 2007; 7: 875–888.
58. Knapp S, Leemans JC, Florquin S, *et al.* Alveolar macrophages have a protective antiinflammatory role during murine pneumococcal pneumonia. *Am J Respir Crit Care Med* 2003; 167: 171–179.
59. Paterson GK, Orihuela CJ. Pneumococci: immunology of the innate host response. *Respirology* 2010; 15: 1057–1063.
60. Schröder NWJ, Morath S, Alexander C, *et al.* Lipoteichoic acid (LTA) of *Streptococcus pneumoniae* and *Staphylococcus aureus* activates immune cells *via* Toll-like receptor (TLR)-2, lipopolysaccharide-binding protein (LBP), and CD14, whereas TLR-4 and MD-2 are not involved. *J Biol Chem* 2003; 278: 15587–15594.
61. Albiger B, Dahlberg S, Sandgren A, *et al.* Toll-like receptor 9 acts at an early stage in host defence against pneumococcal infection. *Cell Microbiol* 2007; 9: 633–644.
62. McNeela EA, Burke A, Neill DR, *et al.* Pneumolysin activates the NLRP3 inflammasome and promotes proinflammatory cytokines independently of TLR4. *PLoS Pathog* 2010; 6: e1001191.
63. Jounai N, Kobiyama K, Takeshita F, *et al.* Recognition of damage-associated molecular patterns related to nucleic acids during inflammation and vaccination. *Front Cell Infect Microbiol* 2012; 2: 168–168.
64. Jiang DH, Liang JR, Noble PW. Hyaluronan as an immune regulator in human diseases. *Physiol Rev* 2011; 91: 221–264.
65. Didierlaurent A, Goulding J, Patel S, *et al.* Sustained desensitization to bacterial Toll-like receptor ligands after resolution of respiratory influenza infection. *J Exp Med* 2008; 205: 323–329.
66. Eddens T, Kolls JK. Host defenses against bacterial lower respiratory tract infection. *Curr Opin Immunol* 2012; 24: 424–430.
67. Wright JR. Immunoregulatory functions of surfactant proteins. *Nat Rev Immunol* 2005; 5: 58–68.
68. Clement CG, Evans SE, Evans CM, *et al.* Stimulation of lung innate immunity protects against lethal pneumococcal pneumonia in mice. *Am J Respir Crit Care Med* 2008; 177: 1322–1330.
69. Murdoch C, Read RC, Zhang Q, *et al.* Choline-binding protein A of *Streptococcus pneumoniae* elicits chemokine production and expression of intercellular adhesion molecule 1 (CD54) by human alveolar epithelial cells. *J Infect Dis* 2002; 186: 1253–1260.
70. Cundell DR, Gerard NP, Gerard C, *et al. Streptococcus pneumoniae* anchor to activated human cells by the receptor for platelet-activating factor. *Nature* 1995; 377: 435–438.
71. Weiser JN, Bae D, Fasching C, *et al.* Antibody-enhanced pneumococcal adherence requires IgA1 protease. *Proc Natl Acad Sci USA* 2003; 100: 4215–4220.
72. Snelgrove RJ, Goulding J, Didierlaurent AM, *et al.* A critical function for CD200 in lung immune homeostasis and the severity of influenza infection. *Nat Immunol* 2008; 9: 1074–1083.
73. Findlay EG, Hussell T. Macrophage-mediated inflammation and disease: a focus on the lung. *Mediators Inflamm* 2012; 140937: 1–6.
74. Janssen WJ, McPhillips KA, Dickinson MG, *et al.* Surfactant proteins A and D suppress alveolar macrophage phagocytosis *via* interaction with SIRP alpha. *Am J Respir Crit Care Med* 2008; 178: 158–167.
75. Guth AM, Janssen WJ, Bosio CM, *et al.* Lung environment determines unique phenotype of alveolar macrophages. *Am J Physiol Lung Cell Mol Physiol* 2009; 296: L936–L946.
76. Hussell T, Cavanagh MM. The innate immune rheostat: influence on lung inflammatory disease and secondary bacterial pneumonia. *Biochem Soc Trans* 2009; 37: 811–813.
77. Davis KM, Nakamura S, Weiser JN. Nod2 sensing of lysozyme-digested peptidoglycan promotes macrophage recruitment and clearance of *S. pneumoniae* colonization in mice. *J Clin Invest* 2011; 121: 3666–3676.
78. Bordon J, Aliberti S, Fernandez-Botran R, *et al.* Understanding the roles of cytokines and neutrophil activity and neutrophil apoptosis in the protective *versus* deleterious inflammatory response in pneumonia. *Int J Infect Dis* 2013; 17: e76–e83.
79. Remmelts HHF, Meijvis SCA, Kovaleva A, *et al.* Changes in serum cortisol levels during community-acquired pneumonia: the influence of dexamethasone. *Respir Med* 2012; 106: 905–908.
80. Kadioglu A, De Filippo K, Bangert M, *et al.* The Integrins Mac-1 and $\alpha_4\beta_1$ perform crucial roles in neutrophil and T cell recruitment to lungs during *Streptococcus pneumoniae* infection. *J Immunol* 2011; 186: 5907–5915.
81. Klesney-Tait J, Keck K, Li X, *et al.* Transepithelial migration of neutrophils into the lung requires TREM-1. *J Clin Invest* 2013; 123: 138–149.
82. Yoshida K, Kondo R, Wang Q, *et al.* Neutrophil cytoskeletal rearrangements during capillary sequestration in bacterial pneumonia in rats. *Am J Respir Crit Care Med* 2006; 174: 689–698.
83. Cundell DR, Gerard C, Idanpaan HI, *et al.* PAf receptor anchors *Streptococcus pneumoniae* to activated human endothelial cells. *Adv Exp Med Biol* 1996; 416: 89–94.
84. Sano H, Kuronuma K, Takahashi H, *et al.* Pulmonary surfactant protein A augments the phagocytosis of *Streptococcus pneumoniae* by alveolar macrophages through a casein kinase 2-dependent increase of cell surface localization of scavenger receptor A. *Trends Glycosci Glycotechnol* 2004; 16: L4–L12.

85. Dorrington MG, Chauvin SE, Tu Z, *et al.* MARCO is required for TLR2- and Nod2-mediated responses to *Streptococcus pneumoniae* and clearance of pneumococcal colonization in the murine nasopharynx. *J Immunol* 2013; 190: 250–258.
86. Gould JM, Weiser JN. Expression of C-reactive protein in the human respiratory tract. *Infect Immun* 2001; 69: 1747–1754.
87. Tino MJ, Wright JR. Surfactant protein A stimulates phagocytosis of specific pulmonary pathogens by alveolar macrophages. *Am J Physiol Lung Cell Mol Physiol* 1996; 270: L677–L688.
88. Hartshorn KL, White MR, Colamussi ML, *et al.* Pulmonary surfactant proteins A and D enhance neutrophil uptake of bacteria. *Am J Physiol Lung Cell Mol Physiol* 1998; 274: L958–L969.
89. Ivanov S, Fontaine J, Paget C, *et al.* Key role for respiratory $CD103^+$ dendritic cells, IFN-γ, and IL-17 in protection against *Streptococcus pneumoniae* infection in response to α-galactosylceramide. *J Infect Dis* 2012; 206: 723–734.
90. Noske N, Hammerschmidt S, Kämmerer U, *et al.* Pneumococcal interaction with human dendritic cells: phagocytosis, survival, and induced adaptive immune response are manipulated by PavA. *J Immunol* 2009; 183: 1952–1963.
91. Rosendahl A, Bergmann S, Hammerschmidt S, *et al.* Lung dendritic cells facilitate extrapulmonary bacterial dissemination during pneumococcal pneumonia. *Front Cell Infect Microbiol* 2013; 3: 21.
92. Khan AQ, Lees A, Snapper CM. Differential regulation of IgG anti-capsular polysaccharide and antiprotein responses to intact *Streptococcus pneumoniae* in the presence of cognate $CD4^+$ T cell help. *J Immunol* 2004; 172: 532–539.
93. Lipsitch M, Whitney CG, Zell E, *et al.* Are anticapsular antibodies the primary mechanism of protection against invasive pneumococcal disease? *PLoS Med* 2005; 2: e15.
94. Gordon SB, Irving GR, Lawson RA, *et al.* Intracellular trafficking and killing of *Streptococcus pneumoniae* by human alveolar macrophages are influenced by opsonins. *Infect Immun* 2000; 68: 2286–2293.
95. Koppel EA, Litjens M, van den Berg, *et al.* Interaction of SIGNR1 expressed by marginal zone macrophages with marginal zone B cells is essential to early IgM responses against *Streptococcus pneumoniae. Mol Immunol* 2008; 45: 2881–2887.
96. Podolsky SH, ed. Pneumonia before Antibiotics: Therapeutic Evolution and Evaluation in Twentieth-Century America. Baltimore, Johns Hopkins University Press, 2006.
97. Aberdein J, Cole J, Bewley M, *et al.* Alveolar macrophages in pulmonary host defence - the unrecognised role of apoptosis as a mechanism of intracellular bacterial killing. *Clin Exp Immunol* 2013; 174: 193–202.
98. McCubbrey AL, Curtis JL. Efferocytosis and lung disease. *Chest* 2013; 143: 1750–1757.
99. Kirby AC, Newton DJ, Carding SR, *et al.* Pulmonary dendritic cells and alveolar macrophages are regulated by gamma delta T cells during the resolution of *S. pneumoniae*-induced inflammation. *J Pathol* 2007; 212: 29–37.
100. Brouwer MC, de Gans J, Heckenberg SG, *et al.* Host genetic susceptibility to pneumococcal and meningococcal disease: a systematic review and meta-analysis. *Lancet Infect Dis* 2009; 9: 31–44.
101. Ram S, Lewis LA, Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. *Clin Microbiol Rev* 2010; 23: 740–780.
102. Brown JS, Hussell T, Gilliland SM, *et al.* The classical pathway is the dominant complement pathway required for innate immunity to *Streptococcus pneumoniae* infection in mice. *Proc Natl Acad Sci USA* 2002; 99: 169–174.
103. Bousfiha A, Picard C, Boisson-Dupuis S, *et al.* Primary immunodeficiencies of protective immunity to primary infections. *Clin Immunol*, 135: 204–209.
104. Chapman SJ, Khor CC, Vannberg FO, *et al.* Common NFKBIL2 polymorphisms and susceptibility to pneumococcal disease: a genetic association study. *Crit Care* 2010; 14: R227.
105. García-Laorden MI, Rodríguez de Castro F, Solé-Violán J, *et al.* The role of mannose-binding lectin in pneumococcal infection. *Eur Respir J* 2013; 41: 131–139.
106. Roy S, Knox K, Segal S, *et al.* MBL genotype and risk of invasive pneumococcal disease: a case-control study. *Lancet* 2002; 359: 1569–1573.
107. Bougle A, Max A, Mongardon N, *et al.* Protective effects of FCGR2A polymorphism in invasive pneumococcal diseases. *Chest* 2012; 142: 1474–1481.
108. Parvaneh N, Casanova JL, Notarangelo LD, *et al.* Primary immunodeficiencies: a rapidly evolving story. *J Allergy Clin Immunol* 2013; 131: 314–323.
109. McCavit TL, Xuan L, Zhang S, *et al.* Hospitalization for invasive pneumococcal disease in a national sample of children with sickle cell disease before and after PCV7 licensure. *Pediatr Blood Cancer* 2012; 58: 945–949.
110. Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. *Lancet* 2011; 378: 86–97.
111. Ezzati M, Kammen D. Indoor air pollution from biomass combustion and acute respiratory infections in Kenya: an exposure-response study. *Lancet* 2001; 358: 619–624.
112. Nuorti JP, Butler JC, Farley MM, *et al.* Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. *N Engl J Med* 2000; 342: 681–689.
113. Mortimer K, Gordon SB, Jindal SK, *et al.* Household air pollution is a major avoidable risk factor for cardiorespiratory disease. *Chest* 2012; 142: 1308–1315.
114. Jambo KC, Sepako E, Fullerton DG, *et al.* Bronchoalveolar $CD4^+$ T cell responses to respiratory antigens are impaired in HIV-infected adults. *Thorax* 2011; 66: 375–382.

115. Hirschtick RE, Glassroth J, Jordan MC, *et al.* Bacterial pneumonia in persons infected with the human immunodeficiency virus. *N Engl J Med* 1995; 333: 845–851.
116. Gordon SB, Molyneux ME, Boeree MJ, *et al.* Opsonic phagocytosis of *Streptococcus pneumoniae* by alveolar macrophages is not impaired in human immunodeficiency virus-infected Malawian adults. *J Infect Dis* 2001; 184: 1345–1349.
117. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 2355–2365.
118. Boikos C, Quach C. Risk of invasive pneumococcal disease in children and adults with asthma: a systematic review. *Vaccine* 2013; 31: 4820–4826.
119. Inghammar M, Engström G, Kahlmeter G, *et al.* Invasive pneumococcal disease in patients with an underlying pulmonary disorder. *Clin Microbiol Infect* 2013 [In press DOI: 10.1111/1469-0691].
120. Joos L, Tamm M. Breakdown of pulmonary host defense in the immunocompromised host: cancer chemotherapy. *Proc Am Thorac Soc* 2005; 2: 445–448.
121. Ek A, Larsson K, Siljerud S, *et al.* Fluticasone and budesonide inhibit cytokine release in human lung epithelial cells and alveolar macrophages. *Allergy* 1999; 54: 691–699.
122. Dinarello CA. Anti-cytokine therapeutics and infections. *Vaccine* 2003; 21: Suppl. 2, S24–S34.
123. O'Brien DP, Nahm MH, Briles DE, *et al.* Tumor necrosis factor alpha receptor I is important for survival from *Streptococcus pneumoniae* infections. *Infect Immun* 1999; 67: 595–601.
124. Vogelgesang A, Grunwald U, Langner S, *et al.* Analysis of lymphocyte subsets in patients with stroke and their influence on infection after stroke. *Stroke* 2008; 39: 237–241.
125. Gordon SB, Miller DE, Day RB, *et al.* Pulmonary immunoglobulin responses to *Streptococcus pneumoniae* are altered but not reduced in human immunodeficiency virus-infected Malawian adults. *J Infect Dis* 2003; 188: 666–670.
126. Eagan R, Twigg HL, French N, *et al.* Lung fluid immunoglobulin from HIV-infected subjects has impaired opsonic function against pneumococci. *Clin Infect Dis* 2007; 44: 1632–1638.
127. Cilloniz C, Polverino E, Ewig S, *et al.* Impact of age and comorbidity on etiology and outcome in community-acquired pneumonia. *Chest* 2013; 144: 999–1007.
128. Rohde GGU. The role of viruses in CAP. *In:* Chalmers JD, Pletz MW, Aliberti S, eds. Community-Acquired Pneumonia. *Eur Respir Monogr* 2014; 63: 74–87.
129. McCullers JA, Rehg JE. Lethal synergism between influenza virus and *Streptococcus pneumoniae*: characterization of a mouse model and the role of platelet-activating factor receptor 1. *J Infect Dis* 2002; 186: 341–350.
130. Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon-gamma during recovery from influenza infection. *Nat Med* 2008; 14: 558–564.
131. Hussell T, Goulding J. Structured regulation of inflammation during respiratory viral infection. *Lancet Infect Dis* 2010; 10: 360–366.
132. Tuder RM, Petrache I. Pathogenesis of chronic obstructive pulmonary disease. *J Clin Invest* 2012; 122: 2749–2755.
133. Fujimori T, Snelgrove R, Hussell T. TAM receptors and their role in the regulation of lung innate immunity. *J Immunol* 2013; 190: 124.29.
134. Kaphalia L, Calhoun WJ. Alcoholic lung injury: metabolic, biochemical and immunological aspects. *Toxicol Lett* 2013; 222: 171–179.
135. Mehta AJ, Yeligar SM, Elon L, *et al.* Alcoholism causes alveolar macrophage zinc deficiency and immune dysfunction. *Am J Respir Crit Care Med* 2013; 188: 716–723.
136. Hyams C, Trzcinski K, Camberlein E, *et al. Streptococcus pneumoniae* capsular serotype invasiveness correlates with the degree of factor H binding and opsonization with C3b/iC3b. *Infect Immun* 2013; 81: 354–363.
137. Hyams C, Camberlein E, Cohen JM, *et al.* The *Streptococcus pneumoniae* capsule inhibits complement activity and neutrophil phagocytosis by multiple mechanisms. *Infect Immun* 2010; 78: 704–715.
138. Wartha F, Beiter K, Albiger B, *et al.* Capsule and D-alanylated lipoteichoic acids protect *Streptococcus pneumoniae* against neutrophil extracellular traps. *Cell Microbiol* 2007; 9: 1162–1171.
139. Shaper M, Hollingshead SK, Benjamin WH J, *et al.* PspA protects *Streptococcus pneumoniae* from killing by apolactoferrin, and antibody to PspA enhances killing of pneumococci by apolactoferrin. *Infect Immun* 2004; 72: 5031–5040.
140. Tu AH, Fulgham RL, McCrory MA, *et al.* Pneumococcal surface protein A inhibits complement activation by *Streptococcus pneumoniae. Infect Immun* 1999; 67: 4720–4724.
141. Ren B, Li J, Genschmer K, *et al.* The absence of PspA or presence of antibody to PspA facilitates the complement-dependent phagocytosis of pneumococci *in vitro. Clin Vaccine Immunol* 2012; 19: 1574–1582.
142. Quin LR, Carmicle S, Dave S, *et al. In vivo* binding of complement regulator factor H by *Streptococcus pneumoniae. J Infect Dis* 2005; 192: 1996–2003.
143. Ogunniyi AD, Grabowicz M, Mahdi LK, *et al.* Pneumococcal histidine triad proteins are regulated by the $Zn2^{+}$-dependent repressor AdcR and inhibit complement deposition through the recruitment of complement factor H. *FASEB J* 2009; 23: 731–738.
144. Beiter K, Wartha F, Albiger B, *et al.* An endonuclease allows *Streptococcus pneumoniae* to escape from neutrophil extracellular traps. *Curr Biol* 2006; 16: 401–407.
145. Dalia AB, Standish AJ, Weiser JN. Three surface exoglycosidases from *Streptococcus pneumoniae*, NanA, BgaA, and StrH, promote resistance to opsonophagocytic killing by human neutrophils. *Infect Immun* 2010; 78: 2108–2116.

146. Brittan JL, Buckeridge TJ, Finn A, *et al.* Pneumococcal neuraminidase A: an essential upper airway colonization factor for *Streptococcus pneumoniae*. *Mol Oral Microbiol* 2012; 27: 270–283.
147. King SJ, Hippe KR, Weiser JN. Deglycosylation of human glycoconjugates by the sequential activities of exoglycosidases expressed by *Streptococcus pneumoniae*. *Mol Microbiol* 2006; 59: 961–974.
148. Jedrzejas MJ. Pneumococcal virulence factors: structure and function. *Microbiol Mol Biol Rev* 2001; 65: 187–207.
149. Agarwal V, Hammerschmidt S, Malm S, *et al.* Enolase of *Streptococcus pneumoniae* binds human complement inhibitor C4b-binding protein and contributes to complement evasion. *J Immunol* 2012; 189: 3575–3584.
150. Bergmann S, Rohde M, Preissner KT, *et al.* The nine residue plasminogen-binding motif of the pneumococcal enolase is the major cofactor of plasmin-mediated degradation of extracellular matrix, dissolution of fibrin and transmigration. *Thromb Haemost* 2005; 94: 304–311.
151. Lammerts Van Bueren A, Ficko-Blean E, Pluvinage B, *et al.* The conformation and function of a multimodular glycogen-degrading pneumococcal virulence factor. *Structure* 2011; 19: 640–651.
152. Nelson AL, Ries J, Bagnoli F, *et al.* RrgA is a pilus-associated adhesin in *Streptococcus pneumoniae*. *Mol Microbiol* 2007; 66: 329–340.
153. Orrskog S, Rounioja S, Spadafina T, *et al.* Pilus adhesin RrgA interacts with complement receptor 3, thereby affecting macrophage function and systemic pneumococcal disease. *MBio* 2012; 4: e00535–12.
154. Paterson GK, Mitchell TJ. The role of *Streptococcus pneumoniae* sortase A in colonisation and pathogenesis. *Microbes Infect* 2006; 8: 145–153.
155. Holmes AR, McNab R, Millsap KW, *et al.* The pavA gene of *Streptococcus pneumoniae* encodes a fibronectin-binding protein that is essential for virulence. *Mol Microbiol* 2001; 41: 1395–1408.
156. Kadioglu A, Brewin H, Hartel T, *et al.* Pneumococcal protein PavA is important for nasopharyngeal carriage and development of sepsis. *Mol Oral Microbiol* 2010; 25: 50–60.
157. Jensch I, Gámez G, Petruschka L, *et al.* PavB is a surface-exposed adhesin of *Streptococcus pneumoniae* contributing to nasopharyngeal colonization and airways infections. *Mol Microbiol* 2010; 77: 22–43.
158. Khan MN, Sharma SK, Filkins LM, *et al.* PcpA of *Streptococcus pneumoniae* mediates adherence to nasopharyngeal and lung epithelial cells and elicits functional antibodies in humans. *Microbes Infect* 2012; 14: 1102–1110.
159. Marriott HM, Mitchell TJ, Dockrell DH. Pneumolysin: a double-edged sword during the host-pathogen interaction. *Curr Mol Med* 2008; 8: 497–509.
160. Knapp S, von Aulock S, Leendertse M, *et al.* Lipoteichoic acid-induced lung inflammation depends on TLR2 and the concerted action of TLR4 and the platelet-activating factor receptor. *J Immunol* 2008; 180: 3478–3484.
161. Brown JS, Ogunniyi AD, Woodrow MC, *et al.* Immunization with components of two iron uptake ABC transporters protects mice against systemic *Streptococcus pneumoniae* infection. *Infect Immun* 2001; 69: 6702–6706.
162. Yesilkaya H, Kadioglu A, Gingles N, *et al.* Role of manganese-containing superoxide dismutase in oxidative stress and virulence of *Streptococcus pneumoniae*. *Infect Immun* 2000; 68: 2819–2826.
163. Park CY, Kim EH, Choi SY, *et al.* Virulence attenuation of *Streptococcus pneumoniae clpP* mutant by sensitivity to oxidative stress in macrophages *via* an NO-mediated pathway. *J Microbiol* 2010; 48: 229–235.
164. Dawid S, Roche AM, Weiser JN. The blp bacteriocins of *Streptococcus pneumoniae* mediate intraspecies competition both *in vitro* and *in vivo*. *Infect Immun* 2007; 75: 443–451.
165. Pericone CD, Overweg K, Hermans PW, *et al.* Inhibitory and bactericidal effects of hydrogen peroxide production by *Streptococcus pneumoniae* on other inhabitants of the upper respiratory tract. *Infect Immun* 2000; 68: 3990–3997.
166. Blomberg C, Dagerhamn J, Dahlberg S, *et al.* Pattern of accessory regions and invasive disease potential in *Streptococcus pneumoniae*. *J Infect Dis* 2009; 199: 1032–1042.
167. McAllister LJ, Ogunniyi AD, Stroeher UH, *et al.* Contribution of serotype and genetic background to virulence of serotype 3 and serogroup 11 pneumococcal isolates. *Infect Immun* 2011; 79: 4839–4849.
168. Silva NA, McCluskey J, Jefferies JM, *et al.* Genomic diversity between strains of the same serotype and multilocus sequence type among pneumococcal clinical isolates. *Infect Immun* 2006; 74: 3513–3518.
169. Trappetti C, van der Maten C, Amin Z, *et al.* Site of isolation determines biofilm formation and virulence phenotypes of *Streptococcus pneumoniae* serotype 3 clinical isolates. *Infect Immun* 2013; 81: 505–513.
170. Obert C, Sublett J, Kaushal D, *et al.* Identification of a candidate *Streptococcus pneumoniae* core genome and regions of diversity correlated with invasive pneumococcal disease. *Infect Immun* 2006; 74: 4766–4777.
171. Sanchez CJ, Hinojosa CA, Shivshankar P, *et al.* Changes in capsular serotype alter the surface exposure of pneumococcal adhesins and impact virulence. *PLoS One* 2011; 6: e26587.
172. Orihuela CJ, Gao G, Francis KP, *et al.* Tissue-specific contributions of pneumococcal virulence factors to pathogenesis. *J Infect Dis* 2004; 190: 1661–1669.
173. Ogunniyi AD, Mahdi LK, Trappetti C, *et al.* Identification of genes that contribute to the pathogenesis of invasive pneumococcal disease by *in vivo* transcriptomic analysis. *Infect Immun* 2012; 80: 3268–3278.
174. Avery OT, Dubos R. The protective action of a specific enzyme against type III pneumococcus infection in mice. *J Exp Med* 1931; 54: 73–89.
175. Weinberger DM, Harboe ZB, Sanders EA, *et al.* Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. *Clin Infect Dis* 2010; 51: 692–699.

176. Hirst RA, Kadioglu A, O'Callaghan C, *et al.* The role of pneumolysin in pneumococcal pneumonia and meningitis. *Clin Exp Immunol* 2004; 138: 195–201.
177. Hammerschmidt S, Wolff S, Hocke A, *et al.* Illustration of pneumococcal polysaccharide capsule during adherence and invasion of epithelial cells. *Infect Immun* 2005; 73: 4653–4667.
178. Weiser JN, Bae D, Epino H, *et al.* Changes in availability of oxygen accentuate differences in capsular polysaccharide expression by phenotypic variants and clinical isolates of *Streptococcus pneumoniae*. *Infect Immun* 2001; 69: 5430–5439.
179. Malley R, Henneke P, Morse SC, *et al.* Recognition of pneumolysin by Toll-like receptor 4 confers resistance to pneumococcal infection. *Proc Natl Acad Sci USA* 2003; 100: 1966–1971.
180. Dessing MC, Hirst RA, de Vos AF, *et al.* Role of Toll-like receptors 2 and 4 in pulmonary inflammation and injury induced by pneumolysin in mice. *PLoS One* 2009; 4: e7993–e7993.
181. Witzenrath M, Pache F, Lorenz D, *et al.* The NLRP3 inflammasome is differentially activated by pneumolysin variants and contributes to host defense in pneumococcal pneumonia. *J Immunol* 2011; 187: 434–440.
182. Harvey RM, Ogunniyi AD, Chen AY, *et al.* Pneumolysin with low hemolytic activity confers an early growth advantage to *Streptococcus pneumoniae* in the blood. *Infect Immun* 2011; 79: 4122–4130.
183. Kirkham LA, Jefferies JM, Kerr AR, *et al.* Identification of invasive serotype 1 pneumococcal isolates that express nonhemolytic pneumolysin. *J Clin Microbiol* 2006; 44: 151–159.
184. Briles DE, Hollingshead SK, Paton JC, *et al.* Immunizations with pneumococcal surface protein A and pneumolysin are protective against pneumonia in a murine model of pulmonary infection with *Streptococcus pneumoniae*. *J Infect Dis* 2003; 188: 339–348.
185. Ogunniyi AD, Folland RL, Briles DE, *et al.* Immunization of mice with combinations of pneumococcal virulence proteins elicits enhanced protection against challenge with *Streptococcus pneumoniae*. *Infect Immun* 2000; 68: 3028–3033.
186. Salha D, Szeto J, Myers L, *et al.* Neutralizing antibodies elicited by a novel detoxified pneumolysin derivative, PlyD1, provide protection against both pneumococcal infection and lung injury. *Infect Immun* 2012; 80: 2212–2220.
187. Kamtchoua T, Bologa M, Hopfer R, *et al.* Safety and immunogenicity of the pneumococcal pneumolysin derivative PlyD1 in a single-antigen protein vaccine candidate in adults. *Vaccine* 2013; 31: 327–333.
188. Anderson R, Steel HC, Cockeran R, *et al.* Comparison of the effects of macrolides, amoxicillin, ceftriaxone, doxycycline, tobramycin and fluoroquinolones, on the production of pneumolysin by *Streptococcus pneumoniae in vitro*. *J Antimicrob Chemother* 2007; 60: 1155–1158.
189. Briles DE, Hollingshead SK, King J, *et al.* Immunization of humans with recombinant pneumococcal surface protein A (rPspA) elicits antibodies that passively protect mice from fatal infection with *Streptococcus pneumoniae* bearing heterologous PspA. *J Infect Dis* 2000; 182: 1694–1701.
190. Barocchi MA, Ries J, Zogaj X, *et al.* A pneumococcal pilus influences virulence and host inflammatory responses. *Proc Natl Acad Sci USA* 2006; 103: 2857–2862.
191. LeMieux J, Hava DL, Basset A, *et al.* RrgA and RrgB are components of a multisubunit pilus encoded by the *Streptococcus pneumoniae* rlrA pathogenicity islet. *Infect Immun* 2006; 74: 2453–2456.
192. Basset A, Zhang F, Benes C, *et al.* Toll-like receptor (TLR) 2 mediates inflammatory responses to oligomerized RrgA pneumococcal pilus type 1 protein. *J Biol Chem* 2013; 288: 2665–2675.
193. Gianfaldoni C, Censini S, Hilleringmann M, *et al. Streptococcus pneumoniae* pilus subunits protect mice against lethal challenge. *Infect Immun* 2007; 75: 1059–1062.
194. Basset A, Trzcinski K, Hermos C, *et al.* Association of the pneumococcal pilus with certain capsular serotypes but not with increased virulence. *J Clin Microbiol* 2007; 45: 1684–1689.
195. Johnsborg O, Håvarstein LS. Regulation of natural genetic transformation and acquisition of transforming DNA in *Streptococcus pneumoniae*. *FEMS Microbiol Rev* 2009; 33: 627–642.
196. Håvarstein LS, Coomaraswamy G, Morrison DA. An unmodified heptadecapeptide pheromone induces competence for genetic transformation in *Streptococcus pneumoniae*. *Proc Natl Acad Sci USA* 1995; 92: 11140–11144.
197. Jackson LA, Neuzil KM, Yu O, *et al.* Effectiveness of pneumococcal polysaccharide vaccine in older adults. *N Engl J Med* 2003; 348: 1747–1755.
198. Gordon SB, Jambo K, Molyneux ME, *et al.* Inhaled delivery of 23-valent pneumococcal polysaccharide vaccine does not result in enhanced pulmonary mucosal immunoglobulin responses. *Vaccine* 2008; 26: 5400–5406.
199. Clutterbuck EA, Lazarus R, Bowman J, *et al.* Pneumococcal conjugate and plain polysaccharide vaccines have divergent effects on antigen-specific B cells. *J Infect Dis* 2012; 205: 1408–1416.
200. Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. *Am J Med* 2008; 121: 219–225.
201. Nie W, Zhang Y, Cheng J, *et al.* Corticosteroids in the treatment of community-acquired pneumonia in adults: a meta-analysis. *PLoS One* 2012; 7: e47926.
202. Waterer GW. Are macrolides now obligatory in severe community-acquired pneumonia? *Intensive Care Med* 2010; 36: 562–564.
203. Doshi SM, Kulkarni PA, Liao JM, *et al.* The impact of statin and macrolide use on early survival in patients with pneumococcal pneumonia. *Am J Med Sci* 2013; 345: 173–177.

204. Steinwede K, Henken S, Bohling J, *et al.* TNF-related apoptosis-inducing ligand (TRAIL) exerts therapeutic efficacy for the treatment of pneumococcal pneumonia in mice. *J Exp Med* 2012; 209: 1937–1952.
205. Bangert M, Bricio-Moreno L, Gore S, *et al.* P4-mediated antibody therapy in an acute model of invasive pneumococcal disease. *J Infect Dis* 2012; 205: 1399–1407.
206. Bangert M, Wright AK, Rylance J, *et al.* Immunoactivating peptide P4 augments alveolar macrophage phagocytosis in two diverse human populations. *Antimicrob Agents Chemother* 2013; 57: 4566–4569.

Chapter 5

Pneumonia due to *Mycoplasma*, *Chlamydophila* and *Legionella*

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SUMMARY: The term "atypical pneumonia" currently identifies pneumonia cases due to *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila*, but this definition is not universally recognised. These infections, together with *Streptococcus pneumoniae*, are the leading cause of pneumonia in outpatients and they are also responsible for hospitalised pneumonia. Due to the fact that these bacteria are naturally resistant to β-lactams, they should be promptly identified, although single clinical or instrumental signs with a sufficient differential diagnostic accuracy have not been described. The use of scoring systems in order to make a weighted evaluation of individual signs and symptoms has been attempted, but results are as yet inconclusive. The use of specific testing (culture, serology and molecular biology) might be useful in identifying a greater number of atypical pneumonia, although each test has important limitations regarding accuracy and feasibility. An approach based on the evaluation of clinical risk associated with the combination of specific tests could be useful for a personalised antibiotic therapy.

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The term "atypical pneumonia" was introduced for the first time by Hobart Reimann in 1938, but had already been used previously to indicate pneumonia cases of unknown cause for which clinical presentation was different from that of pneumococcal lobar pneumonia [1]. During the Second World War, an outbreak of pneumonia with atypical presentation among military recruits of the US army allowed Eaton to identify *Mycoplasma pneumoniae* as the causative agent of atypical pneumonia [2–4]. In 1976, an atypical pneumonia epidemic with severe presentation occurred between the members of a delegation of the American Legion attending a convention in Philadelphia, PA, USA. *Legionella*, a Gram-negative, aerobic bacterium that can replicate in monocytes, was identified as the aetiological agent [5–7]. In 1986, *Chlamydophila pneumoniae*, an obligate intracellular bacterium, was identified as a respiratory pathogen, and *C. pneumoniae* is nowadays recognised as a common respiratory pathogen that may cause atypical pneumonia [8, 9]. In the following years, many other agents have been identified, ranging from viruses to

Table 1. Definitions of atypical pneumonia

Respiratory society	Year of publication	Species included in the definition of ''atypicals''
ATS/IDSA	2007	*Mycoplasma pneumoniae* *Chlamydophila pneumoniae* *Legionella* species Respiratory viruses
BTS	2009	*M. pneumoniae* *C. pneumoniae* *Chlamydophila psittaci* *Coxiella burnetii*
ERS	2011	*M. pneumoniae* *C. pneumoniae* *Legionella* species

ATS: American Thoracic Society; IDSA: Infectious Diseases Society of America; BTS: British Thoracic Society; ERS: European Respiratory Society.

agents of bioterrorism, and currently the definition of atypical pneumonia is not uniformly accepted (table 1).

The British Thoracic Society guidelines emphasise that the term ''atypical'' should not be used in the identification of a specific clinical presentation but it could be useful for clinical management, and defined atypical pneumonia as infections caused by *M. pneumoniae*, *C. pneumoniae*, *Chlamydophila psittaci*, and *Coxiella burnetii*, but not *Legionella* and viruses [10]. The guidelines of the Infectious Diseases Society of America and American Thoracic Society used a broad definition of ''atypical'', including in this term all cases of pneumonia due to agents not detectable on Gram stain or able to be grown on standard bacteriological media [11]. The European Respiratory Society guidelines identified as atypical pneumonia only those cases due to *M. pneumoniae, C. pneumoniae* and *Legionella pneumophila* [12].

MURDOCH and CHAMBERS [13], in an editorial published in *The Lancet* in 2009, proposed the use of the term ''atypical'' only to identify cases of ''new'' pneumonias that required radically different management. Examples include the outbreak of *Legionella* in 1976, cases of *Pneumocystis jirovecii* (previously *Pneumocystis carinii*) pneumonia in 1981, and severe acute respiratory syndrome (SARS) in 2003. Severe cases of pneumonia due to H1N1 influenza A virus in 2009 could be considered as another example of ''atypical'' pneumonia following this type of definition.

The classification system proposed by Murdoch and Chambers is interesting and presents potential possible practical utility; however, for greater adherence to the terminology used in clinical and epidemiological studies throughout the current chapter, ''atypical'' pneumonias will be considered as infections caused by *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila*. These pathogens will be discussed separately, with more detailed descriptions of their epidemiological and clinical features.

M. pneumoniae, *C. pneumoniae* and *L. pneumophila* are responsible for quite an important number of community-acquired pneumonia (CAP) cases. In the vast majority of cases, these infections are of mild to moderate severity, and severe only in a minority of patients; they are intracellular bacteria with natural resistance to β-lactam antibiotics. These features have made it difficult to find a suitable treatment in the past. The advent of new macrolides and quinolones has made treatment more effective, thanks to their good antimicrobial activity and high intracellular concentration. Antibiotic resistance does not represent a clinical problem for atypical bacterial nowadays, but since the year 2000, strains of *Mycoplasma* resistant to macrolides have been isolated in Asia. Recently, an increase in the number of resistant strains was detected in France, suggesting the need for epidemiological monitoring to evaluate clinical impact [14–16].

M. pneumoniae, *C. pneumoniae*, *L. pneumophila* and *Streptococcus pneumoniae* are frequent agents responsible for CAP in outpatients. Macrolides and quinolones are active agents against all these pathogens, and they could represent the ideal choice in the empirical treatment of these patients. However, *S. pneumoniae* macrolide-resistant strains and, less frequently, quinolone-resistant strains, represent clinical concerns and are the first cause of treatment failure in outpatients. Generalised coverage for *M. pneumoniae*, *C. pneumonia* and *L. pneumophila* for every outpatient is not a universal recommendation in the CAP guidelines from different countries, because it would favour a selective pressure and increase resistant strains. Targeted therapy based on clinical risk could be a more reasonable approach to save antibiotics and still ensure adequate treatment [17].

Epidemiology and clinical features of *Chlamydophila* and *Mycoplasma*

M. pneumoniae, *C. pneumoniae* and *S. pneumoniae* are the most frequent cause of CAP in both outpatients and hospitalised patients [18]. The incidence varies from 18.5% to 44–50%; this variability is probably due to the different definitions and laboratory testing used to identify these bacteria in different countries [19].

ARNOLD *et al.* [20] conducted a study using the Community-Acquired Pneumonia Organization (CAPO) database and the University of Louisville (Louisville, KY, USA) infectious disease atypical pathogens reference laboratory database to assess the incidence of *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila* pneumonia. They found that these pathogens are responsible for 20% of the isolates in these databases.

The main age of occurrence of *M. pneumoniae* and *C. pneumoniae* in adults varies from 18 to 45 years, representing 39.7% of the causes of pneumonia in this age range. These patients are significantly younger than patients with pneumonia due to conventional bacteria (mean age 68.9 years) and viruses (mean age 61.9 years) [21, 22]. In a Japanese study, a bimodal age of distribution was found, with a first peak in younger patients, mainly due to *Mycoplasma*, and a second peak in the group aged 60–75 years, mainly due to *Chlamydophila* infection [23]. *Mycoplasma* infection can be found in outbreaks that occur every 3–5 years. Most of these events evolve gradually, but acute spread of the infection could happen in closed communities. Smoking and lower pre-existing specific IgG levels are individual risk factors for *Mycoplasma* infection [24, 25].

Chlamydophila and *Mycoplasma* pneumonia are more frequent in outpatients. Presence of comorbidities is rare and patients generally have a low grade of severity at presentation. Nevertheless, a quarter of patients with pneumonia due to these pathogens required hospitalisation, with a low but not zero hospital mortality (about 5%) [19, 23]. Severe sepsis could have been present in 15% of cases, and 1% of patients needed admission to an intensive care unit (ICU) [21]. Patients with pneumonia due to *Chlamydophila* and *Mycoplasma* are generally poorly symptomatic and they have insidious onset; fever may be absent, and when present is generally around 37.3–37.7°C; severe dyspnoea is rare, but dry cough is frequent, especially in *Mycoplasma* infection. Headache, diarrhoea and other extrapulmonary signs and symptoms are frequent and could guide the diagnosis of these types of pneumonia [19]. The white blood cell count is generally around 7500–8000 cells·μL^{-1} and mean inflammatory markers, such as C-reactive protein (CRP) and procalcitonin (PCT), are generally moderately elevated. Serology could be useful in the aetiological diagnosis, but the test is based on sero-conversion that happens 1–4 weeks after the acute phase of the infection. For these reasons, these tests are more important in epidemiological studies than in daily clinical practice [12].

The new serological tests based on enzymatic immune assay can potentially identify *Mycoplasma* infection using a single determination approximately 7–10 days after the acute phase onset, but false negatives are possible because detectable levels of IgM antibodies are frequently present only 14 days after infection. Furthermore, in adults and in cases of re-infection, IgM antibodies are not always produced [26, 27]. Molecular tests are accurate, but specimen type is very important.

Sputum samples are superior to nasopharyngeal swabs or throat swabs, with a sensitivity of 62.5% and 41.0%, respectively. The greater abundance of *M. pneumoniae* in the pulmonary alveoli compared to the upper respiratory tract could explain this difference [28, 29].

Pneumonia due to these pathogens, if properly treated, generally has a good outcome, with a time to clinical stability of 2 days and a length of hospital stay of 3 days. Around 20% of patients usually require more days of hospitalisation, which is significantly less than the 48% rate for patients with pneumonia due to conventional bacteria [21]. In-hospital mortality is approximately 5%, and 30-day mortality is 1.3%; both outcomes are not significantly different from those of pneumonia due to conventional agents. Nevertheless, the latter more frequently has a more severe presentation and is associated with more comorbidities [21]. Mortality among patients with *Chlamydophila* or *Mycoplasma* pneumonia is possible, but very rare, with only few articles about this topic available in PubMed in 2013, and frequently described as case reports or case series.

Epidemiology and clinical features of *Legionella*

Legionella is responsible for summer outbreaks, sporadic cases and nosocomial infections. Travel could be a risk factor for legionellosis and the European Surveillance Scheme for Travel-Associated Legionnaires' Disease (EWGLINET) reported that about 20% of cases are travel-associated, and that contaminated water in hotels is the main source of infection. During 2008, the highest numbers of cases were reported in France, the UK, Italy and the Netherlands [30].

The main individual risk factors for legionellosis are smoking (>10 cigarettes·day^{-1}), heavy alcohol drinking, chronic bronchitis, diabetes, cancer and corticosteroid therapy [31]. *Legionella* is most frequently responsible for severe cases and it is an important cause of hospitalisation and ICU admission for pneumonia [32]. *Legionella* infection has to be considered in cases of severe presentation with important respiratory involvement, fever $>40^{\circ}$C and CRP >30 mg·dL^{-1}. Radiological findings are not useful to distinguish *Legionella* pneumonia. Homogeneous shadowing is frequent in both Legionnaires' disease and pneumococcal pneumonia, and multilobar presentation and radiographic deterioration are common in bacteraemic pneumococcal pneumonia but also in Legionnaires' disease [33].

The time to clinical stability varies from 4 to 10 days, with an overall mortality of around 10–15%, which rises to 15–30% in patients who required ICU admission [34]. Early diagnosis and early correct treatment are crucial in the outcome of *Legionella* infection. For this reason, sporadic cases are associated with greater mortality because the diagnosis and correct therapy may be delayed, with an increase of mortality from 10% to 30%. Age, female sex, nosocomial cases, ICU stay, renal failure, corticosteroid therapy and high CRP levels are other factors associated with high mortality (table 2) [35]. The use of PCT seems to have a prognostic value in legionellosis: values >1.5 ng·mL^{-1} are predictive of ICU access and mortality [36].

A rapid urinary antigen test is available for the detection of *Legionella*. This test can detect infection of serogroup 1 with a sensitivity of 65–100% and a specificity of 94%, but it cannot detect infections due to other serogroups or species. Serogroup 1 is responsible for 90% of legionellosis in Europe. Different test performances have been reported in the literature, and the Binax test (Binax Alere, Stockport, UK)

Table 2. Factors associated with increased mortality in *Legionella* community-acquired pneumonia

Factor	Relative risk
Age, per 10-year increments	1.50
Female sex	2.00
ICU admission	3.31
Renal failure: serum creatinine 160 μmol·L^{-1} or twice the normal value	2.73
Corticosteroid therapy	2.54
CRP >50 mg·dL^{-1}	2.14

ICU: intensive care unit; CRP: C-reactive protein. Data from [35].

seems to be more sensitive than the Biotest kit (Biotest AG, Dreieich, Germany), with the possibility of detecting serogroups other than serogroup 1 [37]. The urinary antigen test for *Legionella* has had an important clinical impact with a significant increase in the number of cases correctly diagnosed. It is a quick and simple test that allows early correct treatment with better outcomes and reduced case fatality rate [38]. This test seems to have a prognostic value because, as recently shown in the German Competence Network for Community-Acquired Pneumonia (CAPNETZ) study, the degree of positivity of the test correlates with the severity of the disease [39, 40]. A negative aspect is that antigenuria persists for many months after infection and diagnosis of *Legionella* pneumonia in patients with a previous history of infection could be difficult [41]. Molecular tests for *L. pneumophila* are as rapid as the urinary antigen detection test, and also identify serogroups other than 1. The clinical usefulness of this technique could be limited by the fact that sputum is the best sample for testing by PCR, but unproductive cough is a characteristic of atypical pneumonia [42, 43].

The case fatality of legionellosis has decreased over the last few years, probably due to the implementation of rapid diagnostic tests and new guideline recommendations for empirical antibiotic therapy that suggest coverage of *L. pneumophila* for every patient with severe CAP.

Macrolides and fluoroquinolones are the antibiotics of choice for treatment; among these, levofloxacin seems to be more effective than older macrolides (erythromycin and clarithromycin), with a faster time to defervescence (2.0 *versus* 4.5 days), faster time to clinical stability (3 *versus* 5 days) and shorter length of stay (8 *versus* 10 days) but no difference in complication and fatality rate [44, 45]. Azithromycin is probably superior to older macrolides, since an observational study demonstrated the efficacy and safety of the use of azithromycin in legionellosis, with a cure rate of 95% [45, 46]. *In vitro* studies have demonstrated a comparable efficacy against *Legionella* for azithromycin and levofloxacin, but comparative clinical trials are needed to demonstrate any differences in the efficacy of these two important anti-*Legionella* antibiotics [46].

Scoring systems

Scoring systems have been elaborated by several authors and international societies with the aim of differentiating patients with atypical pathogens from pneumonia due to conventional bacteria. On the basis of clinical presentation, no single sign, symptom, radiological or laboratory alteration is sensitive and specific enough to be diagnostic; for these reasons a syndromic approach was proposed.

The syndromic approach is based on the assumption that specific combinations of signs and symptoms and extrapulmonary alterations could suggest or exclude the presence of *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila*. Each of these pathogens has a particular pattern of extrapulmonary involvement that could be used to make a presumptive diagnosis. Otitis, pharyngitis and gastrointestinal involvement suggest a *Mycoplasma* infection, while mental confusion, cardiac and renal involvement with electrolyte abnormalities could suggest a *Legionella* infection.

The main practical problems in the diagnostic work-up of CAP, especially in outpatients, are: 1) differentiating pneumococcal pneumonia from pneumonia due to *M. pneumoniae*, *C. pneumoniae* or *L. pneumophila*, because of different antibiotic susceptibility; and 2) differentiating *Legionella* from *Mycoplasma* and *Chlamydophila* because the former induces severe cases and recrudescence is observed if treatment is interrupted too early.

Distinction of *Chlamydophila* from *Mycoplasma* using clinical elements is more difficult and less important because both are susceptible to the same class of antibiotics, responsible for mild or moderate cases and linked to the same complications, such as the presence of asthma and its exacerbations.

Masiá scoring system for atypical pneumonia identification

Table 3. Masiá experimental scoring system for European countries

Variable	Odds ratio
Exposure to air conditioning	9.09
White blood cell count <10 000 cells·mm^{-3}	7.57
Exposure to birds	3.73
Absence of purulent sputum	3.47
AST <35 U·L^{-1}	2.65
Age <65 years	2.52
Tachypnoea	0.52

Adapted from [19] with permission from the publisher. AST: aspartate aminotransferase.

The scoring system of MASIÁ *et al.* [19] (table 3) is based on the observation that exposure to air conditioning and birds, normal white blood cell count and absence of purulent sputum are common conditions in atypical pneumonia. The score was tested in a European population for the identification of patients with atypical pathogens and showed high specificity (96.7%) but low sensitivity (35%) [19].

Japanese Respiratory Society scoring system for *Mycoplasma* identification

The Japanese Respiratory Society (JRS) guidelines for the management of CAP from the year 2000, and their revision in 2005, classified subjects with mild and moderate pneumonia in patients with or without risk for infections due to *M. pneumoniae*, *C. pneumoniae* or *L. pneumophila*. Patients who meet more than four criteria are at risk of pneumonia due to these pathogens (see criteria in table 4). This distinction was made to limit macrolide use only to patients with mild pneumonia at risk for *M. pneumoniae*, *C. pneumoniae* or *L. pneumophila* infection [48]. In 2011, a survey on the impact of the new JRS guideline on the management of pneumonia was conducted in Japan. The authors concluded that the JRS scoring system has a sensitivity of 77% and a specificity of 93% in the identification of pneumonia due to *M. pneumoniae*, *C. pneumoniae* or *L. pneumophila* and the correct choice for empirical treatment was performed in 80% of cases [49]. Better sensitivity was achieved by the JRS score in the specific identification of *M. pneumoniae* from other causes of pneumonia (sensitivity and specificity of 88.7% and 77.5%, respectively), showing that *M. pneumoniae* cases could be differentiated on the basis of simple clinical findings, easily available in the outpatient context [50].

Winthrop-University Hospital Infectious Disease Division's weighted point system for diagnosing Legionnaires' disease and Winthrop-University Legionnaires' disease diagnostic triad

Table 4. Japanese Respiratory Society scoring system for suspected atypical pneumonia: if more than four items are present, atypical pneumonia could be considered a possible diagnosis

If more than four of the following items are present, atypical pneumonia could be considered as a possible diagnosis
Age <60 years
No underlying disease
Pneumonia outbreaks in the family or community
Paroxysmal cough
Relatively slow pulse rate in relation to the fever
Absence of abnormal chest auscultation
White blood cell count <10 000 cells·mm^{-3}
Ground glass pattern on chest radiograph
No pathogens identified by rapid diagnosis or no sputum

Adapted from [47] with permission from the publisher.

The Winthrop University score was designed specifically to distinguish *Legionella* pneumonia from other forms of pneumonia. This system assigns a score to each item and if the final sum is greater than 15, a diagnosis of legionellosis should be considered. Relative bradycardia (Faget's sign), headache, mental confusion, lack of response to β-lactams,

hypophosphataemia, high levels of CRP and creatine are the elements with highest score in favour of the diagnosis of *Legionella* infection [51].

During the 2009 H1N1 outbreak, a simplified and quickly calculable Winthrop scoring system was proposed (fig. 1). The new Winthrop system starts from the assumption that conventional pneumonia, if not complicated, is characterised by signs and symptoms restricted to the chest; patients with pneumonia and extrapulmonary involvement could be affected by a zoonotic infection or atypical pneumonia. If past history excludes zoonotic infection (Q fever, psittacosis or tularaemia), an atypical pneumonia could be considered and if Faget's sign is present, *Legionella* infection is a probable diagnosis [53–55].

This scoring system also identified *Legionella* cases under unusual circumstances (H1N1 pandemic), thus supporting its clinical utility and suggesting that a clinical syndromic diagnosis of *Legionella* pneumonia is possible [52].

Although not definitive, instruments like the above scores could be useful to identify clinical signs and symptoms suspected for *M. pneumoniae*, *C. pneumoniae* or *L. pneumophila*. The scoring system proposed by the JRS is the most convincing method because it was tested on 1785 patients among 200 Japan hospitals. All but two of the nine items (relatively slow pulse rate in relation to the fever and pneumonia outbreaks in the family or community) differentiate pneumonia due to *Mycoplasma*, *Legionella* and *Chlamydophila* from pneumonia due to other pathogens. The JRS scoring system seems to be most sensitive in the diagnosis of *Mycoplasma*, but these data are based on a quite small group of 105 patients. The scoring system proposed by MASIÁ *et al.* [19] is based on a study of 493 patients, but a sensitivity of 30% seems to be too low for clinical use of this system in clinical practice. The Winthrop scoring system, despite the large number of characteristics assessed and the possible rational basis, has been tested on few patients, and also the interesting feature to distinguish *Legionella* pneumonia and pneumonia due to influenza H1N1 is based on a case series of only nine cases.

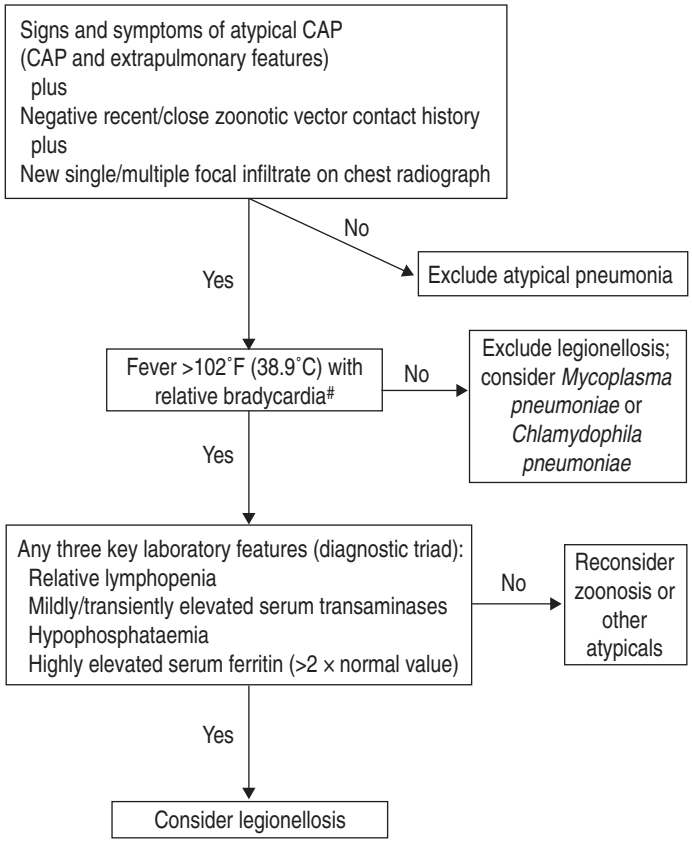

Figure 1. Winthrop-University Hospital Infectious Disease Division's rapid clinical diagnosis of Legionnaires' disease: the Legionnaires' disease diagnostic triad. CAP: community-acquired pneumonia. #: inappropriate pulse response to temperature, with heart rate increase of <10 beats·min^{-1} for each 1°F or 0.5°C temperature elevation. Information from [52].

Conclusions

Infections with atypical organisms are a frequent cause of CAP among outpatients and patients requiring hospitalisation; however, the use of antibiotics against atypical bacteria in every patient with CAP would result in an excessive use of macrolides and quinolones. Furthermore, use of these agents as monotherapy could be a source of failure among outpatients due to the high frequency of *S. pneumoniae*

strains resistant to macrolides in some countries. No single diagnostic test exists for the aetiological diagnosis of pneumonia due to *Mycoplasma*, *Legionella* and *Chlamydophila versus* pneumonia due to other pathogens. Culture, serological tests and PCR are used, but each test has important strengths and weaknesses. Clinical evaluation and integration with a combination of specific diagnostic tests (acute serological evaluation, urinary antigen test and PCR) might allow an aetiological diagnosis and, consequently, a personalisation of antibiotic schemes. Scoring systems are potentially interesting tools for guiding the choice of an empirical therapy, but more data are needed.

Statement of Interest

F. Blasi has received fees outside of the submitted work for board membership from Pfizer, Novartis, GSK, Chiesi, Menarini and Malesci. He has also received fees for consultancy from Chiesi and AstraZeneca and payment for lectures from Pfizer, GSK and Zambon. His institution has received grants from Pfizer, Chiesi and Zambon. M. Mantero has received payment for lectures outside of the submitted work from AstraZeneca, Med Stage Srl and Adveniam.

References

1. Reimann HA. An acute infection of the respiratory tract with atypical pneumonia: a disease entity probably caused by a filtrable virus. *JAMA* 1938; 111: 2377–2384.
2. Epidemiology of atypical pneumonia and acute respiratory disease at Fort Bragg, North Carolina. *Am J Public Health Nations Health* 1944; 34: 335–346.
3. Marmion BP. Eaton agent – science and scientific acceptance: a historical commentary. *Rev Infect Dis* 1990; 12: 338–353.
4. Chanock RM. *Mycoplasma pneumoniae*: proposed nomenclature for atypical pneumonia organism (Eaton agent). *Science* 1963; 140: 662.
5. Fields BS, Benson RF, Besser RE. *Legionella* and Legionnaires' disease: 25 years of investigation. *Clin Microbiol Rev* 2002; 15: 506–526.
6. Fraser DW, Tsai TR, Orenstein W, *et al.* Legionnaires' disease: description of an epidemic of pneumonia. *N Engl J Med* 1977; 297: 1189–1197.
7. McDade JE, Shepard CC, Fraser DW, *et al.* Legionnaires' disease: isolation of a bacterium and demonstration of its role in other respiratory disease. *N Engl J Med* 1977; 297: 1197–1203.
8. Grayston JT, Kuo CC, Wang SP, *et al.* A new *Chlamydia psittaci* strain, TWAR, isolated in acute respiratory tract infections. *N Engl J Med* 1986; 315: 161–168.
9. Marrie TJ, Grayston JT, Wang SP, *et al.* Pneumonia associated with the TWAR strain of *Chlamydia*. *Ann Intern Med* 1987; 106: 507–511.
10. Lim WS, Baudouin SV, George RC, *et al.* BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; 64: Suppl. 3, iii1–iii55.
11. Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44: Suppl. 2, S27–S72.
12. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections – summary. *Clin Microbiol Infect* 2011; 17: Suppl. 6, 1–24.
13. Murdoch DR, Chambers ST. Atypical pneumonia – time to breathe new life into a useful term? *Lancet Infect Dis* 2009; 9: 512–519.
14. Matsuoka M, Narita M, Okazaki N, *et al.* Characterization and molecular analysis of macrolide-resistant *Mycoplasma pneumoniae* clinical isolates obtained in Japan. *Antimicrob Agents Chemother* 2004; 48: 4624–4630.
15. Peuchant O, Menard A, Renaudin H, *et al.* Increased macrolide resistance of *Mycoplasma pneumoniae* in France directly detected in clinical specimens by real-time PCR and melting curve analysis. *J Antimicrob Chemother* 2009; 64: 52–58.
16. Dumke R, von Baum H, Lück PC, *et al.* Occurrence of macrolide-resistant *Mycoplasma pneumoniae* strains in Germany. *Clin Microbiol Infect* 2010; 16: 613–616.
17. de la Campa AG, Ardanuy C, Balsalobre L, *et al.* Changes in fluoroquinolone-resistant *Streptococcus pneumoniae* after 7-valent conjugate vaccination, Spain. *Emerg Infect Dis* 2009; 15: 905–911.
18. Cillóniz C, Ewig S, Polverino E, *et al.* Microbial aetiology of community-acquired pneumonia and its relation to severity. *Thorax* 2011; 66: 340–346.
19. Masiá M, Gutiérrez F, Padilla S, *et al.* Clinical characterisation of pneumonia caused by atypical pathogens combining classical and novel predictors. *Clin Microbiol Infect* 2007; 13: 153–161.
20. Arnold FW, Summersgill JT, Lajoie AS, *et al.* A worldwide perspective of atypical pathogens in community-acquired pneumonia. *Am J Respir Crit Care Med* 2007; 175: 1086–1093.

21. Capelastegui A, España PP, Bilbao A, *et al.* Etiology of community-acquired pneumonia in a population-based study: link between etiology and patients characteristics, process of care, clinical evolution and outcomes. *BMC Infect Dis* 2012; 12: 134.
22. Viasus D, Di Yacovo S, Garcia-Vidal C, *et al.* Community-acquired *Legionella pneumophila* pneumonia: a single-center experience with 214 hospitalized sporadic cases over 15 years. *Medicine (Baltimore)* 2013; 92: 51–60.
23. Goto H. Multicenter surveillance of adult atypical pneumonia in Japan: its clinical features, and efficacy and safety of clarithromycin. *J Infect Chemother* 2011; 17: 97–104.
24. Feikin DR, Moroney JF, Talkington DF, *et al.* An outbreak of acute respiratory disease caused by *Mycoplasma pneumoniae* and adenovirus at a federal service training academy: new implications from an old scenario. *Clin Infect Dis* 1999; 29: 1545–1550.
25. Klement E, Talkington DF, Wasserzug O, *et al.* Identification of risk factors for infection in an outbreak of *Mycoplasma pneumoniae* respiratory tract disease. *Clin Infect Dis* 2006; 43: 1239–1245.
26. Waris ME, Toikka P, Saarinen T, *et al.* Diagnosis of *Mycoplasma pneumoniae* pneumonia in children. *J Clin Microbiol*, 36: 3155–3159.
27. Beersma MF, Dirven K, van Dam AP, *et al.* Evaluation of 12 commercial tests and the complement fixation test for *Mycoplasma pneumoniae*-specific immunoglobulin G (IgG) and IgM antibodies, with PCR used as the ''gold standard''. *J Clin Microbiol* 2005; 43: 2277–2285.
28. Dorigo-Zetsma JW, Verkooyen RP, van Helden HP, *et al.* Molecular detection of *Mycoplasma pneumoniae* in adults with community-acquired pneumonia requiring hospitalization. *J Clin Microbiol* 2001; 39: 1184–1186.
29. Räty R, Rönkkö E, Kleemola M. Sample type is crucial to the diagnosis of *Mycoplasma pneumoniae* pneumonia by PCR. *J Med Microbiol* 2005; 54: 287–291.
30. Ricketts K, Joseph CA, Yadav R, *et al.* Travel-associated Legionnaires' disease in Europe in 2008. *Euro Surveill* 2010; 15: 19578.
31. Dominguez A, Alvarez J, Sabria M, *et al.* Factors influencing the case-fatality rate of Legionnaires' disease. *Int J Tuberc Lung Dis* 2009; 13: 407–412.
32. Sopena N, Sabrià M, Pedro-Botet ML, *et al.* Prospective study of community-acquired pneumonia of bacterial etiology in adults. *Eur J Clin Microbiol Infect Dis* 1999; 18: 852–858.
33. Macfarlane JT, Miller AC, Roderick Smith WH, *et al.* Comparative radiographic features of community acquired Legionnaires' disease, pneumococcal pneumonia, *Mycoplasma* pneumonia, and psittacosis. *Thorax* 1984; 39: 28–33.
34. Falcó V, Fernández de Sevilla T, Alegre J, *et al. Legionella pneumophila.* A cause of severe community-acquired pneumonia. *Chest* 1991; 100: 1007–1011.
35. Chidiac C, Che D, Pires-Cronenberger S, *et al.* Factors associated with hospital mortality in community-acquired legionellosis in France. *Eur Respir J* 2012; 39: 963–970.
36. Haeuptle J, Zaborsky R, Fiumefreddo R, *et al.* Prognostic value of procalcitonin in *Legionella* pneumonia. *Eur J Clin Microbiol Infect Dis* 2009; 28: 55–60.
37. Olsen CW, Elverdal P, Jorgensen CS, *et al.* Comparison of the sensitivity of the *Legionella* urinary antigen EIA kits from Binax and Biotest with urine from patients with infections caused by less common serogroups and subgroups of *Legionella. Eur J Clin Microbiol Infect Dis* 2009; 28: 817–820.
38. Alvarez J, Domínguez A, Sabrià M, *et al.* Impact of the *Legionella* urinary antigen test on epidemiological trends in community outbreaks of legionellosis in Catalonia, Spain, 1990–2004. *Int J Infect Dis* 2009; 13: e365–e370.
39. Blazquez RM, Espinosa FJ, Martinez-Toldos CM, *et al.* Sensitivity of urinary antigen test in relation to clinical severity in a large outbreak of *Legionella* pneumonia in Spain. *Eur J Clin Microbiol Infect Dis* 2005; 24: 488–491.
40. von Baum H, Ewig S, Marre R, *et al.* Community-acquired *Legionella* pneumonia: new insights from the German Competence Network for Community Acquired Pneumonia. *Clin Infect Dis* 2008; 46: 1356–1364.
41. Domínguez J, Galí N, Matas L, *et al.* Evaluation of a rapid immunochromatographic assay for the detection of *Legionella* antigen in urine samples. *Eur J Clin Microbiol Infect Dis* 1999; 18: 896–898.
42. Carrillo JA, Gutiérrez J, García F, *et al.* Development and evaluation of a multiplex test for the detection of atypical bacterial DNA in community-acquired pneumonia during childhood. *Clin Microbiol Infect* 2009; 15: 473–480.
43. Helbig JH, Uldum SA, Lück PC, *et al.* Detection of *Legionella pneumophila* antigen in urine samples by the BinaxNOW immunochromatographic assay and comparison with both Binax *Legionella* Urinary Enzyme Immunoassay (EIA) and Biotest *Legionella* Urine Antigen EIA. *J Med Microbiol* 2001; 50: 509–516.
44. Mykietiuk A, Carratalà J, Fernandez-Sabè N, *et al.* Clinical outcomes for hospitalized patients with *Legionella* pneumonia in the antigenuria era: the influence of levofloxacin therapy. *Clin Infect Dis* 2005; 40: 794–799.
45. Sabrià M, Pedro-Botet ML, Gómez J, *et al.* Fluoroquinolones *vs* macrolides in the treatment of Legionnaires' disease. *Chest* 2005; 128: 1401–1405.
46. Pedro-Botet ML, García-Cruz A, Tural C, *et al.* Severe Legionnaires' disease successfully treated with levofloxacin and azithromycin. *J Chemother* 2006; 18: 559–561.
47. Japanese Respiratory Society. Guidelines for the management of respiratory infections. Differentiating between bacterial pneumonia and atypical pneumonia. *Respirology* 2006; 11: Suppl. 3, S92–S93.
48. Miyashita N, Fukano H, Yoshida K, *et al.* Is it possible to distinguish between atypical pneumonia and bacteria pneumonia? Evaluation of the guidelines for community-acquired pneumonia in Japan. *Respir Med* 2004; 98: 952–960.

49. Kohno S, Seki M, Watanabe A. Evaluation of an assessment system for the JRS 2005: A-DROP for the management of CAP in adults. *Intern Med* 2011; 50: 1183–1191.
50. Yin YD, Zhao F, Ren LL, *et al.* Evaluation of the Japanese Respiratory Society guidelines for the identification of *Mycoplasma pneumoniae* pneumonia. *Respirology* 2012; 17: 1131–1316.
51. Cunha BA. Severe *Legionella* pneumonia: rapid presumptive clinical diagnosis with Winthrop-University Hospital's weighted point score system (modified). *Heart Lung* 2008; 37: 311–320.
52. Cunha BA, Mickail N, Syed U, *et al.* Rapid clinical diagnosis of Legionnaires' disease during the ''herald wave'' of swine influenza (H_1N_1) pandemic: the Legionnaires' disease triad. *Heart Lung* 2010; 39: 249–259.
53. Cunha BA. Pneumonia Essentials. Royal Oak, Physician Press, 2006.
54. Cunha BA. The diagnostic significance of relative bradycardia in infectious disease. *Clin Microbiol Infect* 2000; 6: 633–634.
55. Cunha BA. Atypical pneumonias: current clinical concepts focusing on Legionnaires' disease. *Curr Opin Pulm Med* 2008; 14: 183–194.

Chapter 6

The role of viruses in CAP

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SUMMARY: Viral community-acquired pneumonia (CAP) constitutes approximately 40% of CAP episodes in children and 25% in adults. Respiratory syncytial virus is the most prevalent virus in childhood CAP, whereas in adults influenza plays the most important role. Clinically, viral CAP frequently presents as a disease of gradual onset associated with upper respiratory tract symptoms. Chest pain and leukocytosis are frequently absent compared to bacterial CAP. Co-infection with different respiratory viruses or with bacteria is frequent. In particular, *Streptococcus pneumoniae* as a bacterial pathogen appears to be involved in co-infections. The severity of viral CAP compared to bacterial CAP or mixed CAP is difficult to appraise. However, it seems that in children bacterial CAP appears to be associated with higher mortality, whereas in adults viral CAP is associated with higher mortality. Clearly more research is needed and the increasing availability of molecular diagnostic methods, as well as emerging therapeutic interventions, will contribute to a better understanding of viral CAP.

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It is estimated that approximately 200 million cases of viral community-acquired pneumonia (CAP) occur every year, with a near equal distribution between children and adults [1]. In low- and middle-income countries childhood pneumonia continues to be the leading cause of both morbidity and mortality for young children beyond the neonatal period [2]. Obviously, the identification of the microbiological aetiology of pneumonia is guiding important management and treatment decisions. However, in more than half of the cases an aetiological diagnosis is not possible and treatment decisions largely depend on the clinical presentation of the patient and local experience [3].

The advent of new diagnostic techniques, particularly modern molecular diagnostic tests, has led to improved detection of viruses in CAP and has subsequently also greatly increased our understanding of the role of viruses in pneumonia [1]. Improved knowledge about the true prevalence of respiratory viruses as aetiological pathogens will probably lead to improved management of CAP in the future [3].

The spectrum of respiratory viruses differs according to age (children, adults and the elderly), as well as the place of treatment (community setting, nursing home or intensive care unit (ICU)). Moreover, multiple viral infections, as well as viral–bacterial co-infections, have to be considered [1].

Another important issue is the perception that viral infections are synonymous with nonsevere disease. However, viral CAP can be associated with significant mortality. For example, adenoviruses (AdV) can cause severe disease [4] and fatal cases of adenoviral CAP have been reported. This is true for AdV types 3 [5] and 11 [6]. Moreover, influenza virus infection clearly leads to additional mortality worldwide [7]. Recently it has been shown that more than one-third of ICU patients with CAP have evidence of viral infection [8].

This chapter summarises the progress made in the field of viral CAP within the past 5 years and updates the current knowledge on the diagnosis of viral CAP, the estimated prevalence of viral CAP in children and adults, and the frequency of viral–viral and viral–bacterial co-infections, as well as the outcome of viral CAP.

How to diagnose viral CAP

It is very difficult to diagnose viral CAP on the basis of clinical parameters alone. In 2000 an attempt was made to create a clinical algorithm in order to identify bacterial CAP from atypical CAP (including, but not restricted to, viruses). Independent predictors related to bacterial pneumonia were an acute onset of disease, age >65 years or comorbidity, and leukocytosis or leukopenia. Sensitivity and specificity of a scoring system computed on the basis of these findings to identify patients with bacterial pneumonia were 89% and 94%, respectively. The prediction rule developed from these three variables classified the aetiology of pneumonia with an area under the receiver operating characteristic (ROC) curve of 0.84 [9].

In partial accordance, JOHNSTONE *et al.* [10] later reported that patients with viral infections are older, more likely to have underlying cardiac disease and frailer. Differences in clinical presentation included a low frequency of chest pain and a normal leukocyte count, which again is in accordance with the previous findings. Viral infections occurred between October and May, whereas bacterial infections occurred throughout the year [10]. Recently, data from larger prospective and multicentre studies became available. A Chinese study in CAP outpatients found that the presence of cough, dyspnoea, absence of chest pain and a white blood cell count between 4.0 cells·L^{-1} and 10.0×10^9 cells·L^{-1} were associated with viral CAP, which are again in accordance with earlier findings. However, the accuracy level for aetiological diagnosis was low (area under ROC curve 0.61) [11]. In addition, the most recent study on this topic identified absence of leukocytosis as an independent predictor of viral pneumonia [12]. Nursing home residence was another independent predictor. A recent large Spanish multicentre study on adults with CAP also described clinical features of bacterial and viral CAP. Viral CAP patients more frequently presented with rhinorrhoea (22% *versus* 8%) and had leukocytosis (30% *versus* 63%), pleuritic chest pain (23% *versus* 38%) and co-morbidities less frequently (60% *versus* 79%), but had multilobar disease more frequently (62% *versus* 33%) [13]. A summary of factors associated with viral CAP is presented in table 1.

The advent of PCR largely improved the diagnostic sensitivity in viral CAP, especially for respiratory viruses that are difficult to culture, such as human rhinoviruses. However, positive PCR results do not always prove infection is present, as has recently been shown for human bocavirus (hBoV) infection. In Salvador, Brazil, 277 children with CAP were prospectively studied and hBoV DNA was detected in 62 (23%) out of 268 nasopharyngeal aspirates while 156 (57%) out of 273 were seropositive. Acute primary hBoV infection was reliably diagnosed (bearing at least two acute markers: positive IgM, a four-fold increase/conversion of IgG, low IgG avidity or viraemia) in only 21 (8%) of these 273 patients, even though 83% had a high DNA load [14].

Table 1. Factors associated with viral community-acquired pneumonia

Season between October and May
Gradual onset of disease
Rhinorrhoea
Cough
Absence of chest pain
Multi-lobar disease
Normal leukocyte count

The choice of sample type also plays an important role. Whereas sputum is thought to be the most suitable sample type for bacterial culture, it seems that for the detection of viruses in CAP upper air samples, such as oropharyngeal samples, represent a valid alternative to lower airway samples such as sputum, which often is difficult to obtain [15].

What is the prevalence of viral CAP?

In order to answer this question a PubMed search was performed, which was restricted to studies published within the past 5 years (September 2008 to September 2013), using the following search strategy: ''viral'' AND ''community'' AND ''acquired'' AND ''pneumonia''. Earlier studies are well summarised and commented on in the review by MARCOS *et al.* [16]. 284 PubMed hits were obtained and all abstracts were screened by the author and, if eligible, the full text was analysed. Only studies including immunocompetent patients were included. Diagnosis of CAP needed to include chest radiography, including in children. Furthermore, only studies on seasonal respiratory viruses were considered, thus influenza H5N1, H7N9, severe acute respiratory syndrome virus, Middle East respiratory syndrome coronavirus and other pandemic viruses were not considered. Influenza H1N1pdm09 was considered in the analysis if included in viral panels together with other respiratory viruses. Studies had to be prospective and include a minimum of 75 patients. Studies needed to specify exactly which viruses were tested and also needed to report individual results for each specific virus. In order to determine the prevalence, frequencies of detection were documented and/or recalculated from the results presented. Frequencies of detection presented in tables 2 and 3 were always related to the complete number of patients investigated. In the case that different virus species were reported they were grouped together under the genus name.

Children

13 studies covering 7118 children fulfilling the criteria specified above were identified. In 4184 (58.8%) of those an aetiological diagnosis was achieved and 2937 (41.3%) were associated with viral detection. There was a wide range of PCR positivity (14.1–73.5%). In most of the studies respiratory syncytial virus (RSV) was the most frequent pathogen [6] followed by human rhinoviruses (hRV) [5]. In one study, AdV were the most frequent. However, not all studies investigated hRVs, which are difficult to detect (mainly by PCR only), or some of the other viruses, whereas nearly all studies looked for RSV. Details of these studies are presented in table 2.

In a series of systematic reviews, not included in table 2, RUDAN *et al.* [2] determined the incidence of childhood CAP in low- and middle-income countries in 2010 using the World Health Organization's definition to be approximately 0.22 episodes per child-year, with 11.5% of cases progressing to severe episodes. RSV was the most common pathogen (29%), followed by influenza (17%) [2]. A short summary of the individual studies according to continent is provided below.

Europe

A recent large prospective Italian single centre study involved 592 children with radiographically confirmed CAP using molecular techniques (17 viruses). A total of 435 (73.5%) out of 592 children were positive for at least one virus, while the most frequently detected virus was RSV (31.8%), followed by hRV (24.3%), hBoV (10.1%), influenza viruses (9.6%) and human metapneumovirus (hMPV) (8.3%) [17]. An earlier serological study from Italy investigated 101 children admitted for CAP. 50 (50%) had confirmation of a viral pathogen confirming RSV as the most prevalent virus in this country [28]. Two prospective studies from the UK conducted in 2001–2002 and 2009–2011, comprising a total of 401 hospitalised children aged 0–16 years with radiologically confirmed pneumonia, supported the finding that RSV was the most frequent virus. Viruses were detected in 37.5% of patients

[18]. A large Spanish, single centre, 6-year prospective study mainly supported these findings. The most frequently detected virus was RSV (30.5%) followed by hRV (19.2%), hBoV (13.1%), AdV (13.1%), hMPV (8.2%) and parainfluenza virus (5.3%). Interestingly, the rate of viral detection was significantly greater in infants aged <18 months (83%) than in older children (67%) ($p<0.001$) [22]. A Finnish study analysed induced sputum samples of 76 children hospitalised for pneumonia for 18 viruses by antigen detection and PCR. Viruses were found in 72% of samples. In this study hRV were the most frequently detected viruses (30%). Other prevalent viruses were hBoV (18%) and hMPV (14%), RSV was only detected in 6.6% [23].

Asia

A very large study from Cambodia investigated 959 children with CAP. 135 (14.1%) tested positive for viruses by multiplex PCR. hRV were most frequent (7.1%) followed by human coronaviruses (hCoV) (1.9%) and influenza (1.7%). RSV (2.4%) and hMPV (0.7%) were infrequent [19].

A prospective single centre study from Taiwan determined the presence of respiratory viruses using conventional techniques (serology, IF and cultures) in children admitted for CAP. 87 (41.6%) out of 209 children were virus positive (AdV: 18%, parainfluenza virus: 15.7%, influenza: 14.1%, and RSV: 12.4%). Importantly many relevant respiratory viruses such as hRV were not investigated in this study [21]. OKADA *et al.* [24] enrolled 903 children with CAP into a prospective multicentre study in Japan using PCR and culture for the detection of respiratory viruses. 469 (51.9%) were virus positive. RSV (22.9%) and hRV (16.6%) were by far the most frequent viruses followed by parainfluenza virus (7.4%), hBoV (4.8%) and AdV (1.6%). hMPV was very infrequent (0.2%) [24]. A Chinese study specifically investigated the newly described hRV C, together with types A and B in children hospitalised with CAP in Beijing. The authors collected nasopharyngeal aspirates from 554 children and used RT-PCR and sequencing for viral detection. Infections with other respiratory viruses were identified by PCR. hRV were detected in 99 (17.9%) patients, of which 51.52% tested for hRV-A, 38.38% for hRV-C and 10.10% for hRV-B. Co-infections with other respiratory viruses were detected in 57.58% of the hRV-positive children [25]. Another Chinese study prospectively investigated microbiological aetiology in children hospitalised for CAP. Methods were serology, blood culture and a nasopharyngeal aspirate for viral antigen testing; 821 cases were included. Microbial aetiology for CAP was identified in 547 (67%) children; viral in 353 (43%), bacterial in 228 (27%), mixed viral bacterial in 107 (13%), dual viral in 10 (1%) and concurrent bacterial in 10 (1%). RSV was the most prevalent virus (18%), followed by influenza (9%), AdV (8%) and parainfluenza virus (8%) [26]. A study from Israel investigated nasopharyngeal wash specimens from children aged <5 years evaluated in the emergency department with radiologically diagnosed CAP specifically for hMPV by RT-PCR and also for RSV, AdV, influenza and parainfluenza virus by direct immunofluorescence and culture. In this study hMPV was detected in 108 (8.3%) out of 1296 patients *versus* RSV in 23.1%, AdV in 3.4%, influenza A in 2.9% and parainfluenza virus in 2.9%; hRV were not assessed [29].

America

WIEMKEN *et al.* [20] investigated the role of respiratory viruses in severe CAP patients admitted to the ICU in the USA. In their multicentre trial using a nasopharyngeal swab and multiplex PCR (Luminex xTAG), 14 (18.7%) out of 75 paediatric patients were virus positive. The most frequent viruses were hRV (9.3%), influenza (4%) and hMPV (2.7%) [20]. A Brazilian study investigated nasopharyngeal aspirate and blood from 184 children with radiologically proven CAP. 111 children were virus positive with hRV being the most prevalent (21%) virus followed by parainfluenza virus (17%) and RSV (15%). Interestingly, a marked seasonal variation was observed with frequent parainfluenza virus detection during spring and frequent RSV detection during the autumn [27].

Table 2. Aetiology of viral community-acquired pneumonia in children

First author [ref.]	Year	Country	Design	Sample types	Total patients	Techniques used	Positive patients#	Total viruses of positive patients	Influenza virus A and B	RSV	hRV	hMPV	hBoV	PIV	hCoV	AdV
Esposito [17]	2013	Italy	Prospective single centre study	NPS, blood	592	Multiplex PCR (17 viruses)	435 (73.5)	435 (73.5)	57 (9.6)	**188 (31.8)**	144 (24.3)	49 (8.3)	60 (10.1)	11 (1.9)	33 (5.6)	11 (1.9)
Elemraid [18]	2013	UK	Prospective multicentre study	Blood, NPA, NPS, TBS, pleural fluid	401	IF, PCR, multiplex PCR	225 (56.1)	150 (37.4)	31 (7.7)	**63 (15.7)**	12 (3)	1 (0.3)	4 (1)	11 (2.7)	3 (0.8)	23 (5.7)
Vong [19]	2013	Cambodia	Prospective multicentre study	Blood, spontaneous sputum, throat swab, NPS	959	Multiplex PCR and culture	449 (46.8)	135 (14.1)	16 (1.7)	23 (2.4)	**68 (7.1)**	7 (0.7)	0	0	18 (1.9)	0
Wiemken [20]	2012	USA	Prospective multicentre study	NPS	75	Multiplex PCR	14 (18.7)	14 (18.7)	3 (4)	¶	**7 (9.3)**	2 (2.7)	ND	¶	ND	¶
Chen [21]	2012	Taiwan	Prospective single centre study	Blood, pleural fluid, urine, sputum, OPS,	209	Serology, IF, cultures,	178 (85.2)	87 (41.6)	25 (14.1)	22 (12.4)	ND	ND	ND	28 (15.7)	ND	**32 (18)**
Garcia-Garcia [22]	2012	Italy	Prospective single centre study	NPA	884	PCR (16 viruses)	649 (73.4)	649 (73.4)	45 (5.1)	**270 (30.5)**	170 (19.2)	46 (8.2)	116 (13.1)	47 (5.3)	12 (1.4)	116 (13.1)
Honkinen [23]	2012	Finland	Prospective single centre study	Induced sputum	76	IF and PCR (18 viruses, culture)	74 (91)	55 (72)	3 (4)	5 (6.6)	**23 (30.3)**	11 (14.5)	14 (18.4)	6 (7.9)	5 (6.6)	8 (10.5)
Okada [24]	2012	Japan	Prospective multicentre study	NPS	903	PCR and culture	737 (81.6)	469 (51.9)	18 (2)	**207 (22.9)**	150 (16.6) + 18 entero-viruses	2 (0.2)	43 (4.8)	67 (7.4)	ND	14 (1.6)

Table 2. Continued

First author [ref.]	Year	Country	Design	Sample types	Total patients	Techniques used	Positive patients[#]	Total viruses of positive patients	Influenza virus A and B	RSV	hRV	hMPV	hBoV	PIV	hCoV	AdV
XIANG [25]	2010	China	Prospective single centre study	NPA	554	Multiplex PCR, single PCR, Sequencing	99 (17.9)	99 (17.9)	ND	39 (39.4)	**99 (100)[+]**	1 (1)	5 (5.1)	10 (10.1)	2 (2)	6 (6.1)
ZHANG [26]	2011	China	Prospective single centre study	NPA, blood	884	Serology, blood culture, antigen test, IF	547 (67)	353 (43)	75 (9)	**149 (18)**	ND	ND	ND	62 (8)	ND	67 (8)
NASCIMENTO-CARVALHO [27]	2010	Brazil	Prospective single centre study	NPA, blood	184	Serology, PCR, antigen test	144 (78)	111 (60)	16 (9)	27 (15)	**38 (21) + 9 (5) entero-viruses**	ND	ND	31 (17)	ND	5 (3)
DON [28]	2009	Italy	Prospective single centre study	Blood	101	Serology	75 (75)	50 (50)	ND	**17 (17)**	ND	5 (5)	ND	12 (12)	ND	ND
WOLF [29]	2009	Israel	Prospective single centre study	NPW	1296	PCR, IF, culture	608 (47)	608 (47)	37 (2.9)	**300 (23.1)**	ND	108 (8.3)	ND	37 (2.9)	ND	44 (3.4)
Total					7118		4183 (58.8)	2937 (41.3)								

Data are presented as n, n (%) or n (% total number of patients). Bold data indicates the highest number. RSV: respiratory syncytial virus; hRV: human rhinovirus; hMPV: human metapneumovirus; hBoV: human bocavirus; PIV: parainfluenza viruses (1–4), hCoV: human coronaviruses; AdV: adenoviruses; NPS: nasopharyngeal swab; NPA: nasopharyngeal aspirate; TBS: tracheobronchial secretions; OPS: oropharyngeal secretion; NPW: nasopharyngeal wash; IF: immunofluorescence; ND: not done. [#]: single and mixed; [¶]: virus included in panel but no results reported; [+]: other viruses were only investigated in hRV positive patients.

Table 3. Aetiology of viral community-acquired pneumonia (CAP) in adults

Study	Year	Country	Design	Sample types	Total patients	Techniques used	Positive patients#	Total viruses of positive patients	Influenza virus A and B	RSV	hRV	hMPV	hBoV	PIV	hCoV	AdV
Liu [11]	2013	China	Prospective multicentre study	Throat swab, spontaneous sputum, blood	500	Multiplex PCR for 15 viruses, bacterial culture, blood cultures	271 (54.2)	182 (36.4)	**112 (24.2)**	7 (1.4)	21 (4.2) + 3 (0.7) entero-virus	10 (2)	ND	32 (6.4)	4 (0.8)	25 (5)
Takahashi [30]	2013	Vietnam	Prospective CAP surveillance study	Blood, sputum, NPS	174	PCR for 13 viruses, culture	27 (15.5)	27 (15.5)	**10 (8.6)**	1 (0.5)	9 (5.2)	0	0	0	0	3 (1.8)
Luchsinger [31]	2013	Chile	Prospective two centre study	Blood, induced sputum, NPA	356	Culture, serology, PCR	232 (65.2)	140 (39.3)	27 (7.6)	**48 (13.2)**	41 (11.5)	41 (11.5)	ND	ND	20 (5.6)	3 (0.8)
Viasus [13]	2013	Spain	Prospective multicentre study	BAL, NPS, blood, spontaneous sputum, urine	747	PCR, culture, UAT	315 (42.2)	161 (21.6)	**107 (14.3)**	3 (0.4)	19 (2.5)	0	ND	4 (0.5)	0	0
Musher [32]	2013	USA	Prospective single centre study	Blood, spontaneous sputum, NPS	215	Multiplex PCR for 15 viruses	96 (44.7)	42 (19.5)	1 (0.5)	3 (1.4)	**26 (12.1)**	3 (1.4)	ND	4 (1.9)	7 (3.3)	0
Ma [12]	2013	China	Prospective single centre study	Spontaneous sputum, NPA	488	Culture, IF, serology	137 (28.1)	51 (10.5)	**30 (6.2)**	16 (3.3)	ND	ND	ND	5 (1)	ND	ND
Huijskens [33]	2013		Netherlands	Prospective single centre study	Throat swab, blood, sputum, urine	408	PCR, culture, UAT, serology	265 (64.5)	**117 (28.7)**	32 (7.8)	8 (2)	34 (8.3)	<1	<1	23 (5.6)	23 (5.6)
Wiemken [20]	2012	USA	Prospective multicentre study	NPS	393	Multiplex PCR	92 (23.4)	92 (23.4)	**38 (9.7)**	+	33 (8.4)	13 (3.3)	ND	+	ND	+

Table 3. Continued

Study	Year	Country	Design	Sample types	Total patients	Techniques used	Positive patients[#]	Total viruses of positive patients	Influenza virus A and B	RSV	hRV	hMPV	hBoV	PIV	hCoV	AdV
SANGIL [34]	2012	Spain	Prospective single centre study	Blood, NPS, urine	131	Culture, PCR, UAT, serology	92 (70.2)	47 (35.9)	7 (5.3)	10 (7.6)	**13 (10.0)**	4 (3.1)	0	4 (3.1)	7 (5.3)	0
MERMOND [35]	2010	New Caledonia	Prospective single centre study	Spontaneous sputum, TBA, BAL, PSB, pleural fluid, blood, urine	137	Culture, PCR, serology, urine antigen tests	82 (59.8)	30 (36.6)	**26 (31.7)**	1 (1.2)	ND	ND	ND	2 (2.4)	ND	1 (1.2)
CAO [36]	2010	China	Prospective single centre study	Spontaneous sputum, throat swab	197	PCR	102 (51.8)	28 (14.2)	**12 (11.9)**	2 (2)	2 (2)	2 (2)	ND	5 (5)	1 (1)	5 (5)
LIEBERMAN [37]	2010	Israel	Prospective single centre study	OPS, NPS, NPW	183	Mutiplex TaqMan PCR	58 (31.7)	58 (31.7)	8 (4.4)	13 (7.1)	9 (4.9)	2 (1.1)	ND	0	**24 (13.1)**	3 (1.6)
JOHANSSON [38][¶]	2010	Sweden	Prospective single centre study	NPA, induced sputum, blood, urine	184	Monoplex and duplex real-time PCR, culture, serology, urine antigen tests	124 (67)	53 (29)	**14 (8)**	7 (4)	12 (7) + 1 (0.5%) entero-virus	4 (2)		7 (4)	4 (2)	3 (2)
Total					4113		1893 (46.0)	1028 (25.0)	**8**	1	3				1	

Data are presented as n, n (%) or n (% total number of patients). Bold data indicates the highest number. RSV: respiratory syncytial virus; hRV: human rhinovirus; hMPV: human metapneumovirus; hBoV: human bocavirus; PIV: parainfluenza viruses (1–4), hCoV: human coronaviruses; AdV: adenoviruses; NPS: nasopharyngeal swab; NPA: nasopharyngeal aspirate; BAL: bronchoalveolar lavage; TBA: tracheobronchial aspirate; PSB: protected specimen brush; OPS: oropharyngeal secretion; NPW: nasopharyngeal wash; UAT: urinary antigen test; IF: immunofluorescence; ND: not done. [#]: single and mixed; [¶]: two patients were positive for herpes simplex virus 1 (1%); [+]: virus included in panel but no results reported.

Adults

Similar to the situation in children, 13 studies were identified. In total 4113 adult patients with CAP were investigated in these studies. In 1893 (46.0%) patients an aetiological diagnosis could be made and 1028 (25.0%) patients were virus positive. Influenza viruses was the most prevalent virus [8], followed by hRV [3], RSV [1] and coronavirus [1]. However, not all studies investigated all viruses, in particular hRV and coronavirus were not always tested for. Details of the studies mentioned can be found in table 3. Below is a short summary of the individual studies according to continent.

Europe

In the European studies, influenza and hRV were mainly detected. A prospective multicentre study from Spain investigated a total of 747 adults with CAP requiring hospitalisation. The aetiology was determined in 315 (42.2%) patients, in whom 154 (21.9%) were due to bacteria, 125 (16.7%) were due to viruses and 36 (4.8%) were mixed (due to viruses and bacteria) [13]. Influenza was the most prevalent virus (14.3%) followed by hRV (2.5%), parainfluenza virus (0.5%) and RSV (0.4%). Another Spanish study found that 92 (70.2%) out of 131 patients were virus infected. Interestingly, the most frequent viruses in this analysis were hRV (10%). Influenza only ranked third (5.3%) after RSV (7.6%) [34]. A study from the Netherlands investigated 408 hospitalised patients and identified 117 (28.7%) virus-positive patients. Also in this study hRV (8.3%) were the most prevalent, closely followed by influenza (7.8%), parainfluenza virus and coronavirus (both 5.6%). RSV (2%), hMPV and hBoV (both $<$1%) occurred infrequently [33]. Within the German Competence Network for Community-Acquired Pneumonia (CAPNETZ) the incidence, clinical characteristics, and outcome of patients with influenza-associated CAP was studied prospectively in 5032 patients and compared to patients without influenza. 160 patients with influenza-associated CAP were identified (12% of those with defined aetiology) from which 34 (21%) patients had a concomitant pathogen (mostly *Streptococcus pneumoniae*) [39]. A Swedish study with the ultimate goal to investigate the added value of extensive aetiological investigation including the new molecular techniques, prospectively included 184 adults admitted for CAP during a 12-month period. In this study again hRV were the most prevalent [38].

Asia

In most studies influenza was identified as the most prevalent virus. A recent multicentre study from China included 500 adult CAP outpatients and used multiplex and quantitative real-time fluorescence PCR to detect 15 respiratory viruses and *Mycoplasma pneumoniae*, respectively. In this study the pathogen detection rate was 54.2% with viruses accounting for 36.4%, *M. pneumoniae* for 18.0% and bacteria for 14.4%. Influenza A was the most frequent pathogen in this cohort (18.4%) [11]. Another Chinese study in elderly patients (aged $\geqslant$65 years) that aimed to define predictors of viral CAP investigated aetiology of hospitalised CAP using conventional techniques (without PCR). In this study, 51 (10.5%) patients were virus positive, mostly for influenza viruses (6.2%), followed by RSV (3.3%) and parainfluenza virus (1%). No other viruses were investigated [12]. A third Chinese study prospectively studied sputum and throat swabs of 197 outpatients with CAP and found a pathogen in nearly 52%. Of the patients, 14% were positive for respiratory viruses, again influenza viruses (12% of the whole population) were most frequent, followed by parainfluenza virus (5%) and AdV (5%) [36]. A prospective surveillance study from central Vietnam included 174 patients hospitalised for CAP, of which 27 tested positive for viruses. The most prevalent virus again was influenza (8.6%), followed by hRV (5.2%) and AdV (1.8%) [30]. LIEBERMAN *et al.* [37] performed a study in 183 hospitalised patients with CAP in Israel using three different sampling techniques (oropharyngeal samples, nasopharyngeal swab and nasopharyngeal wash) for the diagnosis of viral CAP by multiplex TaqMan PCR covering 12 relevant respiratory viruses. 58 (31.7%) patients were virus positive. In contrast to the other studies hCoV was the most frequent virus (13.1%) followed by RSV (7.1%), hRV (7.1%) and influenza viruses (4.4%) [37].

America

In America the situation is heterogeneous. In Chile, 356 patients were prospectively investigated and 80 (22%) cases with a single viral pathogen and 60 (17%) cases with mixed bacterial and viral infection were identified [31]. RSV was the most frequent virus (13.5%) followed by hMPV (11.5%) and hRV (11.5%). Influenza (7.6%) and hCoV (5.6%) occurred less frequently. Most of the patients were hospitalised (n=330) [31]. A prospective single centre study from the USA of hospitalised CAP patients enrolled 215 patients and detected respiratory viruses using a commercial multiplex PCR assay in 42 (19.5%) patients. The most frequent virus was hRV (12.1%) followed by hCoV (3.3%), parainfluenza virus (1.9%), hMPV (1.4%) and RSV (1.4%) [32]. Another study from the USA investigated severe CAP patients admitted to ICU. In this multicentre trial, using nasopharyngeal swabs and multiplex PCR (Luminex xTAG), 92 (23.4%) out of 393 patients were virus positive. The most frequent viruses were influenza (9.7%), hRV (8.4%) and hMPV (3.3%) [20].

Other regions

A recent study from New Caledonia, a French archipelago in the South Pacific, investigated 137 patients with CAP. In 82 (59.8%) of these the aetiology could be confirmed. 117 pathogens were detected: *S. pneumoniae* was the most common (41.0%), followed by influenza virus A (22.1%) and *Haemophilus influenzae* (10.2%). The frequency of atypical bacteria was low (6.0%). The most frequent and significant co-infection was *S. pneumoniae* with influenza A virus (p=0.004) [35].

Co-infection

Co-infection, either bacterial–viral or viral–viral, has been observed in clinical practice for a long time, particularly in children [40]. The following section will try to summarise the progress made within the field of co-infection in relation to children and adults.

Children

Viral–viral co-infection was frequent in a recent Italian study on children with radiologically proven CAP (117 (26.9%) out 435 virus positive children). In a large Chinese single centre study, nasopharyngeal aspirates were collected from 1028 children diagnosed with CAP. Samples were investigated for hMPV and common respiratory viruses by PCR. hMPV was detected in 6.3% of patients. Co-infections with other respiratory viruses were detected in 70.8%, mainly RSV (41.5%) or rhinovirus (38.5%) [41]. In a large Italian study of 884 children with CAP, viral–viral co-infection was observed in 30% [22].

Viral–bacterial co-infection was also studied in several studies from different countries. A Taiwanese study in children with CAP identified mixed infections in 85 (41%) out of the 209 cases. 69 (33%) cases were viral–bacterial co-infection, including 36 cases with *S. pneumoniae*, 29 cases with *M. pneumoniae* and nine cases with chlamydial infection. Interestingly, again 59.3% of the 86 cases with *S. pneumoniae* infection were co-infected with other pathogens, including *M. pneumoniae* in 18 (20.9%) cases, chlamydia in seven (8.1%) cases and viral agents in 36 (41.9%) cases [21]. In a large Japanese study on viral CAP in 903 children, 158 (33.7%) out of 469 virus-positive patients were co-infected with bacteria. In particular, hRV-positive (62.3%) and hBoV-positive (55.3%) patients also showed proof of bacterial infection [24]. A Finnish study investigating 76 children hospitalised for pneumonia found bacterial–viral co-infection in 66%. Rhinovirus co-infection with *S. pneumoniae* was the most commonly found combination of virus and bacterium (16%). Two viruses were found in 22% of samples and three in 8% [23].

These new data support the hypothesis that co-infection occurs frequently in children and that it is particularly prevalent in *S. pneumoniae* infections.

Adults

There are several studies investigating co-infections in adults, with most reporting both viral–viral as well as viral–bacterial co-infections. In a large Chinese multicentre study, the co-infection rate was 13.4% (67 out of 500). In the 182 viral adult CAP patients, 219 different virus strains were observed. Most of the co-infections were viral–viral. In this study no clear associations were reported between specific viruses and bacteria [11]. A study from Chile reported bacterial–viral co-infection in 60 (17%) out of 356 adult CAP patients, mainly in patients with *S. pneumoniae* or *M. pneumoniae*. Interestingly, 50% of patients infected with *S. pneumoniae* were co-infected with viruses [31]. In a large study from Spain 36 out of 747 patients showed mixed infections. These adult patients presented more frequently with hypoxaemia (55.4%) and high-risk CURB65 (confusion, urea >7 mmol·L^{-1}, respiratory rate $\geqslant 30$ breaths·min^{-1}, blood pressure <90 mmHg (systolic) or $\leqslant 60$ mmHg (diastolic), age $\geqslant 65$ years) (63.9%). Amongst the predictors for severe disease were infection with influenza A (H1N1)pdm09 and influenza B, but also with *Streptococcus* spp. [13]. A Dutch study of 408 adult CAP patients reported that in 16 out 117 virus-positive patients multiple virus infection was identified. Parainfluenza viruses were the most frequently detected viruses in multiple viral infection. Bacterial/viral co-infection was common in *S. pneumoniae* (53 (38.1%) out of 139), and *H. influenzae* (11 (52.4%) out of 21) infection. Actually, these relationships were both statistically significant [33]. In a Spanish analysis the incidence of bacterial co-infection in adult influenza A H1N1 CAP during the pandemic period was 33% [42]. Another Spanish study detected bacterial–viral co-infection in 25 (19.1%) out of 131 patients. The most frequent combination was hRV and *S. pneumoniae* (n=8, 6.1%), followed by coronavirus and *S. pneumoniae* (n=4, 3.1%), and RSV and *S. pneumoniae* (n=3, 2.3%) [34].

A study from the Karolinska institute in Solna, Sweden, found that patients infected with a virus and a bacterial pathogen develop severe CAP more often and have a longer period of hospitalisation than those with a bacterial aetiology alone. The authors prospectively investigated 184 adults with CAP and reported that the likelihood of getting a score corresponding to Pneumonia Severity Index classes IV or V was higher in patients with findings of both bacteria and virus than in those with a bacterial pathogen alone (OR 4.98, 95% CI 2.09–11.89; $p<0.001$) [43].

What is the outcome of viral CAP?

Different outcomes can be considered in viral CAP. This section concentrates on measures of severity and mortality and their relationship to aetiological diagnosis in CAP.

Severity

A recent study from Chile investigating 356 patients with CAP did not find any relationship between infection classification (bacteria, virus or mixed co-infection) and illness severity outcome as defined by the Fine Score. In addition, the presence of multiple pathogens did not contribute to more severe disease [31]. In contrast, a Spanish study (n=131) compared severity of viral (n=22) and bacterial (n=45) CAP and found that bacterial CAP showed significantly higher CURB65 scores (1.4 *versus* 0.7, p=0.02) and significantly more frequent shock (18% *versus* 0%, p=0.04) [34]. Similar conclusions were drawn by RUDAN *et al.* [2] in their series of systematic reviews. The authors found that at the level of severe episodes, RSV contribution decreased from 28.8% to 22.6% and influenza from 17.0% to 7.0%, while *S. pneumoniae* increased from 6.9% to 18.3% and *H. influenzae* type b from 2.8% to 4.1% [2]. Another Spanish multicentre study in adults described higher Pneumonia Severity Index and CURB-65 classes in patients with bacterial pneumonia as compared to viral pneumonia (58% *versus* 40% and 48% *versus* 27%, respectively) [13]. Interestingly rates of ICU admission (33% *versus* 12%), need for mechanical ventilation (24% *versus* 6%) and acute respiratory distress syndrome (22% *versus* 7%) were higher in viral CAP, which was mainly

influenza A (H1N1)pdm09. In accordance with this an ICU-based study found that one-third of CAP was associated with detection of respiratory viruses [8].

There is no clear picture at the moment. Some studies showed increased severity of bacterial CAP whereas others found this to be true for viral CAP. Many reasons can be contemplated but these differences in findings will mainly relate to the populations studied, the diagnostic methods used and the definition of severity.

Mortality

In the series of systematic reviews by RUDAN *et al.* [2] it was shown that bacterial aetiologies became more important in the subgroup of children who eventually died of the disease. The authors found that the dominant aetiological pathogens in children dying from CAP were *S. pneumoniae* (32.7%) and *H. influenzae* type b (15.7%) [2]. In contrast, the previously mentioned Spanish multicentre study found higher in-hospital mortality in viral CAP compared to bacterial CAP (18% *versus* 7%) [13]. However, in this study a high prevalence of influenza A (H1N1)pdm09 may have largely contributed to these figures. Partly in line with this, a Dutch study found a significantly higher mortality in mixed bacterial and viral infection [44]. In patients admitted to the ICU with severe CAP there was no difference in mortality in bacterial CAP compared to viral CAP [8]. It seems that in children bacterial CAP is associated with higher mortality whereas in adults viral CAP seems to be associated with higher mortality.

Conclusions

Viral infection constitutes an important aetiology in CAP. Around 40% of CAP in children and 25% in adults has been found to be associated with viruses. RSV is the most prevalent virus in childhood CAP whereas in adults influenza plays the most important role. The clinical presentation of viral CAP is different compared to bacterial CAP. Usually, the onset is less abrupt, upper respiratory tract symptoms are present, and chest pain and leukocytosis are frequently absent. However, these clinical parameters still have insufficient predictive value. The advent of molecular techniques allowed viral infection to be more sensitively detected and greatly contributed to a better understanding of their role. However, in research settings serology still can be of added value. Most studies used upper respiratory tract specimens for diagnosis and, for viruses, this seems a valid choice. However, one has to keep in mind that mixed bacterial and viral infections are prevalent and for bacterial detection a lower respiratory tract sample is important. Most frequently, viral co-infection has been found in *S. pneumoniae* bacterial CAP. However, *S. pneumoniae* is the most frequent bacterial pathogen in CAP and thus it is not clear whether this really represents an independent association. Viral–viral co-infection was also frequently reported. Data on outcome of viral CAP still are heterogeneous. This is probably mainly due to the individual characteristics of the viruses investigated. In particular, influenza A (H1N1)pdm09 was associated with increased severity and higher mortality which influenced many studies reporting outcome.

In summary, there still is a need to better understand the real incidence, prevalence and outcome of viral CAP worldwide. To date, most studies are single centre studies. The Pneumonia Etiology Research for Child Health (PERCH) project is a seven country, standardised, comprehensive evaluation of the aetiological agents causing severe pneumonia in children from developing countries [45]. Similar initiatives for adult patients are warranted.

Statement of Interest

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References

1. Ruuskanen O, Lahti E, Jennings LC, *et al.* Viral pneumonia. *Lancet* 2011; 377: 1264–1275.
2. Rudan I, O'Brien KL, Nair H, *et al.* Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. *J Glob Health* 2013; 3: 10401.
3. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. *Clin Infect Dis* 2011; 52: Suppl. 4, S296–S304.
4. Clark TW, Fleet DH, Wiselka MJ. Severe community-acquired adenovirus pneumonia in an immunocompetent 44-year-old woman: a case report and review of the literature. *J Med Case Rep* 2011; 5: 259.
5. Girouard G, Garceau R, Thibault L, *et al.* Province-wide adenovirus type 3 outbreak with severe cases in New Brunswick. *Can J Infect Dis Med Microbiol* 2011; 22: e4–e6.
6. Gu L, Liu Z, Li X, *et al.* Severe community-acquired pneumonia caused by adenovirus type 11 in immunocompetent adults in Beijing. *J Clin Virol* 2012; 54: 295–301.
7. Clark NM, Lynch JP 3rd. Influenza: epidemiology, clinical features, therapy, and prevention. *Semin Respir Crit Care Med* 2011; 32: 373–392.
8. Choi SH, Hong SB, Ko GB, *et al.* Viral infection in patients with severe pneumonia requiring intensive care unit admission. *Am J Respir Crit Care Med* 2012; 186: 325–332.
9. Ruiz-Gonzalez A, Falguera M, Vives M, *et al.* Community-acquired pneumonia: development of a bedside predictive model and scoring system to identify the aetiology. *Respir Med* 2000; 94: 505–510.
10. Johnstone J, Majumdar SR, Fox JD, *et al.* Viral infection in adults hospitalized with community-acquired pneumonia: prevalence, pathogens, and presentation. *Chest* 2008; 134: 1141–1148.
11. Liu YF, Gao Y, Chen MF, *et al.* Etiological analysis and predictive diagnostic model building of community-acquired pneumonia in adult outpatients in Beijing, China. *BMC Infect Dis* 2013; 13: 309.
12. Ma HM, Lee KP, Woo J. Predictors of viral pneumonia: the need for viral testing in all patients hospitalized for nursing home-acquired pneumonia. *Geriatr Gerontol Int* 2013; 13: 949–957.
13. Viasus D, Marinescu C, Villoslada A, *et al.* Community-acquired pneumonia during the first post-pandemic influenza season: a prospective, multicentre cohort study. *J Infect* 2013; 67: 185–193.
14. Nascimento-Carvalho CM, Cardoso MR, Meriluoto M, *et al.* Human bocavirus infection diagnosed serologically among children admitted to hospital with community-acquired pneumonia in a tropical region. *J Med Virol* 2012; 84: 253–258.
15. Huijskens EG, Rossen JW, Kluytmans JA, *et al.* Evaluation of yield of currently available diagnostics by sample type to optimize detection of respiratory pathogens in patients with a community-acquired pneumonia. *Influenza Other Respir Viruses* 2013 [In press DOI: 10.1111/irv.12153].
16. Marcos MA, Esperatti M, Torres A. Viral pneumonia. *Curr Opin Infect Dis* 2009; 22: 143–147.
17. Esposito S, Daleno C, Prunotto G, *et al.* Impact of viral infections in children with community-acquired pneumonia: results of a study of 17 respiratory viruses. *Influenza Other Respir Viruses* 2013; 7: 18–26.
18. Elemraid MA, Sails AD, Eltringham GJ, *et al.* Aetiology of paediatric pneumonia after the introduction of pneumococcal conjugate vaccine. *Eur Respir J* 2013; 42: 1595–1603.
19. Vong S, Guillard B, Borand L, *et al.* Acute lower respiratory infections in $\geqslant$5 year-old hospitalized patients in Cambodia, a low-income tropical country: clinical characteristics and pathogenic etiology. *BMC Infect Dis* 2013; 13: 97.
20. Wiemken T, Peyrani P, Bryant K, *et al.* Incidence of respiratory viruses in patients with community-acquired pneumonia admitted to the intensive care unit: results from the Severe Influenza Pneumonia Surveillance (SIPS) project. *Eur J Clin Microbiol Infect Dis* 2013; 32: 705–710.
21. Chen CJ, Lin PY, Tsai MH, *et al.* Etiology of community-acquired pneumonia in hospitalized children in northern Taiwan. *Pediatr Infect Dis J* 2012; 31: e196–e201.
22. Garcia-García ML, Calvo C, Pozo F, *et al.* Spectrum of respiratory viruses in children with community-acquired pneumonia. *Pediatr Infect Dis J* 2012; 31: 808–813.
23. Honkinen M, Lahti E, Österback R, *et al.* Viruses and bacteria in sputum samples of children with community-acquired pneumonia. *Clin Microbiol Infect* 2012; 18: 300–307.
24. Okada T, Morozumi M, Sakata H, *et al.* A practical approach estimating etiologic agents using real-time PCR in pediatric inpatients with community-acquired pneumonia. *J Infect Chemother* 2012; 18: 832–840.
25. Xiang Z, Gonzalez R, Xie Z, *et al.* Human rhinovirus C infections mirror those of human rhinovirus A in children with community-acquired pneumonia. *J Clin Virol* 2010; 49: 94–99.
26. Zhang Q, Guo Z, MacDonald NE. Vaccine preventable community-acquired pneumonia in hospitalized children in Northwest China. *Pediatr Infect Dis J* 2011; 30: 7–10.
27. Nascimento-Carvalho CM, Cardoso MR, Barral A, *et al.* Seasonal patterns of viral and bacterial infections among children hospitalized with community-acquired pneumonia in a tropical region. *Scand J Infect Dis* 2010; 42: 839–844.
28. Don M, Söderlund-Venermo M, Valent F, *et al.* Serologically verified human bocavirus pneumonia in children. *Pediatr Pulmonol* 2010; 45: 120–126.
29. Wolf DG, Greenberg D, Shemer-Avni Y, *et al.* Association of human metapneumovirus with radiologically diagnosed community-acquired alveolar pneumonia in young children. *J Pediatr* 2010; 156: 115–120.

30. Takahashi K, Suzuki M, Minh le N, *et al.* The incidence and aetiology of hospitalised community-acquired pneumonia among Vietnamese adults: a prospective surveillance in Central Vietnam. *BMC Infect Dis* 2013; 13: 296.
31. Luchsinger V, Ruiz M, Zunino E, *et al.* Community-acquired pneumonia in Chile: the clinical relevance in the detection of viruses and atypical bacteria. *Thorax* 2013; 68: 1000–1006.
32. Musher DM, Roig IL, Cazares G, *et al.* Can an etiologic agent be identified in adults who are hospitalized for community-acquired pneumonia: results of a one-year study. *J Infect* 2013; 67: 11–18.
33. Huijskens EG, van Erkel AJ, Palmen FM, *et al.* Viral and bacterial aetiology of community-acquired pneumonia in adults. *Influenza Other Respir Viruses* 2013; 7: 567–573.
34. Sangil A, Calbo E, Robles A, *et al.* Aetiology of community-acquired pneumonia among adults in an H1N1 pandemic year: the role of respiratory viruses. *Eur J Clin Microbiol Infect Dis* 2012; 31: 2765–2772.
35. Mermond S, Berlioz-Arthaud A, Estivals M, *et al.* Aetiology of community-acquired pneumonia in hospitalized adult patients in New Caledonia. *Trop Med Int Health* 2010; 15: 1517–1524.
36. Cao B, Ren LL, Zhao F, *et al.* Viral and *Mycoplasma pneumoniae* community-acquired pneumonia and novel clinical outcome evaluation in ambulatory adult patients in China. *Eur J Clin Microbiol Infect Dis* 2010; 29: 1443–1448.
37. Lieberman D, Shimoni A, Shemer-Avni Y, *et al.* Respiratory viruses in adults with community-acquired pneumonia. *Chest* 2010; 138: 811–816.
38. Johansson N, Kalin M, Tiveljung-Lindell A, *et al.* Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. *Clin Infect Dis* 2010; 50: 202–209.
39. von Baum H, Schweiger B, Welte T, *et al.* How deadly is seasonal influenza associated pneumonia? The German Competence Network for Community-acquired pneumonia. *Eur Respir J* 2011; 37: 1151–1157.
40. Korppi M. Mixed microbial aetiology of community-acquired pneumonia in children. *APMIS* 2002; 110: 515–522.
41. Lu G, Li J, Xie Z, *et al.* Human metapneumovirus associated with community-acquired pneumonia in children in Beijing, China. *J Med Virol* 2013; 85: 138–143.
42. Cillóniz C, Ewig S, Menéndez R, *et al.* Bacterial co-infection with H1N1 infection in patients admitted with community acquired pneumonia. *J Infect* 2012; 65: 223–230.
43. Johansson N, Kalin M, Hedlund J. Clinical impact of combined viral and bacterial infection in patients with community-acquired pneumonia. *Scand J Infect Dis* 2011; 43: 609–615.
44. Diederen BM, Van Der Eerden MM, Vlaspolder F, *et al.* Detection of respiratory viruses and *Legionella* spp. by real-time polymerase chain reaction in patients with community acquired pneumonia. *Scand J Infect Dis* 2009; 41: 45–50.
45. Levine OS, O'Brien KL, Deloria-Knoll M, *et al.* The Pneumonia Etiology Research for Child Health Project: a 21st century childhood pneumonia etiology study. *Clin Infect Dis* 2012; 54: Suppl. 2, S93–S101.

Chapter 7

Severity assessment tools in CAP

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SUMMARY: Community-acquired pneumonia (CAP) remains a leading cause of death worldwide and a major burden on healthcare resources. CAP may vary in severity, from a mild disease managed in the community to a very severe illness requiring hospital or intensive care unit (ICU) admission. Illness severity is not always obvious at presentation and therefore a range of severity assessment tools have been developed to aid clinical decision making. Severity assessment tools have been proven to aid the site of care decision, increasing the proportion of low-risk patients managed at home. Most severity tools were initially developed to predict mortality risk, and recent validation studies have demonstrated that risk of death is not always a good indicator for ICU care. Other severity scores have been developed recently with the aim to predict ICU admission or other clinical decisions. The introduction of biomarkers as prognostic indicators of severe CAP, whether used alone or in conjunction with other clinical severity of illness scores, is a promising area for future research. There remains no consensus on which is the best severity assessment tool in CAP. The most recent and relevant data regarding clinical prediction tools and biomarkers to predict severity in CAP are reviewed in this chapter.

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The severity of illness and mortality rate of community-acquired pneumonia (CAP) varies widely, from less than 1% in patients managed in the community, to a reported mortality rate of 5–15% in hospitalised patients [1–3]. Mortality may be as high as 25% in patients requiring mechanical ventilation and near 50% in patients also requiring vasopressor support [3, 4].

Accurate severity assessment of CAP is, therefore, critical for determining site of care and has also been proposed as a useful way to guide different antibiotic and adjunctive therapies. Approximately 10% of CAP hospitalised patients require intensive care unit (ICU) care [5], representing one of the most common causes of ICU admission internationally [6]. The decision of where to treat a patient with CAP is crucial, impacting on clinical outcomes and hospital costs [7].

Recognising the importance of disease severity in these decisions, multiple severity assessment tools have been developed for CAP. Most of these severity criteria are based on similar clinical prediction tools such as demographics, comorbid conditions, and physiological, laboratory and

imaging parameters [8–18]. In addition, several promising prognostic biomarkers have recently been evaluated suggesting that these may be used alone, or in conjunction with clinical scores to aid clinical decisions.

This chapter reviews the evidence for severity assessment tools and prognostic biomarkers in guiding the management of CAP.

Prediction tools: what are we trying to predict?

In considering the available severity assessment tools, it is important to keep in mind the end-point which the tool was designed to predict. Severity assessment tools have been used to predict a range of clinical events including 30-day mortality [8–11], long-term mortality [19], ICU admission [13, 14], complicated parapneumonic effusions/empyema [20] and bacteraemia [21]. They have been recommended by guidelines or studies to guide the site of care decision [9], empirical antibiotic prescribing [22], and the intensity of microbiological work-up and follow-up [9, 22].

Not surprisingly, the predictors of each of these end-points are not the same, and so tools that predict mortality will not necessarily predict ICU admissions or complications. The definition of "severe CAP" therefore remains poorly defined and persists as a matter of controversy and debate [23, 24].

The reason for this is complex, but reflects the fact that mortality from pneumonia is not always directly related to severity. MORTENSEN *et al.* [25] demonstrated, in an analysis of the PORT (Patient Outcomes Research Team) cohort studies results, that up to half of all deaths in patients with pneumonia occurred due to comorbid conditions rather than being directly due to pneumonia. This is important, as ICU admission or a change of antibiotic therapy is unlikely to modify these outcomes. In an analysis of 39 895 deaths from pneumonia in a nationwide German study, less than a quarter of patients dying had received ventilatory support [26], illustrating the fact that most patients with pneumonia die with treatment restrictions, such as do not attempt resuscitation orders, in place [27].

Therefore, while mortality is a very useful end-point, there is a growing consensus that to identify patients most likely to benefit from intensive treatment strategies, the most useful end-point is the requirement for mechanical ventilation or vasopressor support due to respiratory failure or septic shock [28]. This is preferred to simply using ICU admission as an end-point because ICU admission rates vary substantially between different healthcare systems, being higher in North America and lower in Europe [29, 30]. Preventing patients from deteriorating to the point of needing respiratory or vasopressor support is critical, because of the very high mortality rates reported where such patients are initially managed as "nonsevere" CAP [31, 32]. However, it should not be assumed that hospitalising such patients in the ICU earlier would necessarily lead to survival. In a confidential inquiry into pneumonia deaths in young adults in the UK published in 2000, it was concluded that the vast majority of deaths could not be prevented with the currently available therapies, including ICU care [33].

It has been shown that scores, to date, are poorly predictive of microbial aetiology of pneumonia, with both typical and atypical bacteria being present in low- and high- severity CAP [34], such that using severity assessment tools to guide empirical antibiotic prescribing currently has limited evidence to support it [35].

The perfect severity score or biomarker does not yet exist, but would predict all of the end-points shown in figure 1. More importantly, scores need to identify patients that will benefit from intensified treatment, monitoring or novel therapies. Although the choice of tools varies, severity assessment tools of some kind are recommended by nearly every major national and international CAP guideline [9, 12, 22, 35–37].

This chapter will focus primarily on scores to predict mortality, ICU admission, mechanical ventilation and vasopressor support.

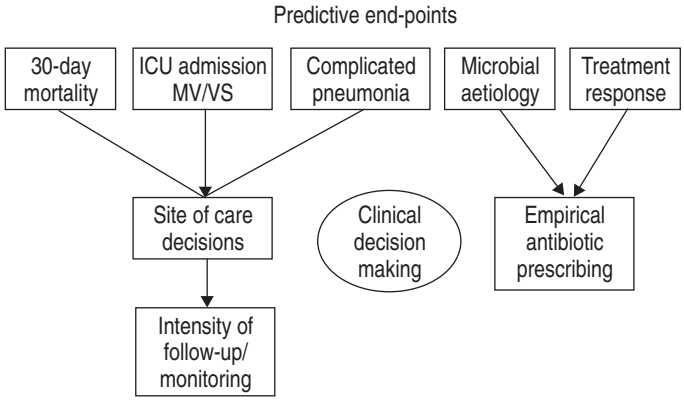

Figure 1. End-points and clinical applications of severity scores in community-acquired pneumonia. ICU: intensive care unit; MV: mechanical ventilation; VS: vasopressor support.

Clinical scores

There is evidence that physicians using their clinical judgment may both overestimate and underestimate the severity of CAP [38, 39]. Severity scores may resolve these difficulties by providing objective classification of patients into the different risk categories [40]. With this aim, multiple clinical assessment tools have been developed in recent years to predict severity in CAP.

The most well recognised and widely used are the Pneumonia Severity Index (PSI) [8] and the CURB65 (confusion, urea >7 mmol·L^{-1}, respiratory rate $\geqslant 30$ breaths·min^{-1}, blood pressure <90 mmHg (systolic) or $\leqslant 60$ mmHg (diastolic), age $\geqslant 65$ years) score [11]. Although they are recommended by current international guidelines, these scores have important limitations arising from the use of 30-day mortality as an outcome. Subsequently, therefore, a number of alternative scores have been developed with improved predictive characteristics for ICU admission and, more specifically, mechanical ventilation or vasopressor support [13–16]. In addition, the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) 2007 guidelines have also proposed a severity score to define the requirement for ICU admission [9]. The specific scores are described below and summarised in table 1.

Pneumonia Severity Index

The PSI is a 20-point score that classifies patients into five risk categories, and was developed in 1997 by FINE *et al.* [8]. It uses three demographic parameters (age, sex and nursing home residence), comorbidities (congestive heart failure, cerebrovascular disease, cancer, renal disease and liver disease), five physical examination findings (tachypnoea, tachycardia, blood pressure, confusion and temperature) and complementary results from laboratory tests and imaging. The objective of this tool is to identify patients at low risk of death who can receive outpatient care safely (class I–II). It has also been shown that a proportion of patients in class III without evidence of oxygen desaturation can be managed as outpatients. Calculation of the PSI and a typical protocol are shown in figure 2.

The PSI score was initially designed to predict patients' risk of 30-day mortality, for which it has been validated with a moderate to good accuracy [8, 41]. It has been successfully applied in clinical practice to increase the use of outpatient treatment in CAP [42]. Five studies have been described in which the PSI was used to increase the proportion of patients treated in the community. These include a before and after intervention in the USA [43], a controlled critical pathway intervention in Canada [44], a randomised controlled trial in Spain [45], a controlled observational study in France [46] and a large cluster randomised controlled trial in the USA [47]. Despite the diversity of these interventions, all showed that implementing the PSI resulted in a substantial reduction in hospital admissions, with an odds ratio of 2.31 (95% CI 2.03–2.63) when pooled in a meta-analysis (0% heterogeneity). This provides very strong evidence that use of the severity score improves site of care decisions in clinical practice.

Despite this, the PSI has important limitations that should be considered. It is heavily weighted by age and comorbid conditions, and the large number of variables makes it complex to use [48]. In addition, validation studies in predicting requirement for ICU care have detected low sensitivity

Table 1. Selected scoring systems for prognosis in community-acquired pneumonia

Scoring system	Recommended applications	AUC for mortality[#]	AUC for ICU admission	Strengths	Weaknesses
PSI	Site of care	0.81[¶]	0.56–0.79	Well validated Useful for research Proven to improve site of care decisions in intervention studies	Complex to use Does not predict ICU admission Heavily weighted by age Poorly predictive in young patients
CURB65	Site of care Empirical antibiotic choice ICU admission	0.80[¶]	0.60–0.78	Well validated Simple to calculate	Poorly predictive of ICU admission Underestimates severity in young patients Limited evidence of clinical impact
CRB65	Hospitalisation decision Site of care	0.79[¶]	0.57–0.77	As for CURB65	As for CURB65 Also limited data from primary care
IDSA/ATS 2007 criteria	ICU admission	0.78–0.88	0.80–0.88	Well validated Excellent prediction of ICU admission and 30-day mortality Relatively simple to use Based on physiological variables	Limited evidence of impact on clinical practice
SMART-COP	ICU admission	0.71–0.85	0.72–0.87	Excellent prediction of ICU admission and 30-day mortality Based on physiological variables	Relatively complex to calculate Limited independent validation Limited evidence of impact on clinical practice
SCAP rule	ICU admission Site of care	0.75–0.78	0.72–0.86	Improved prediction of ICU admission compared to PSI/CURB65	Limited validation No evidence of impact on clinical practice
REA-ICU	ICU admission	0.74–0.78	0.76–0.80	Improved prediction of ICU admission compared to PSI/CURB65	Limited independent validation No evidence of impact on clinical practice
CAP-PIRO	Prediction of outcome in ICU admitted patients	0.88	NA	Only score specifically developed for ICU admitted patients	Lack of independent validation
Biomarkers	Antibiotic prescribing	Dependent on marker (see text)	Dependent on marker (see text)	Physiological Additive to clinical scores May predict aetiology	Cost Requirement for specialised assays or equipment Limited validation of most markers

AUC: area under the receiver operator characteristic curve; ICU: intensive care unit; PSI: Pneumonia Severity Index; CURB65: confusion, urea >7 mmol·L^{-1}, respiratory rate $\geqslant 30$ breaths·min^{-1}, blood pressure <90 mmHg (systolic) or $\leqslant 60$ mmHg (diastolic), age $\geqslant 65$ years; CRB65: confusion, respiratory rate $\geqslant 30$ breaths·min^{-1}, blood pressure <90 mmHg (systolic) or $\leqslant 60$ mmHg (diastolic), age $\geqslant 65$ years; IDSA: Infectious Diseases Society of America; ATS: American Thoracic Society; SMART-COP: systolic blood pressure, multilobar chest radiograph involvement, albumin, respiratory rate, tachycardia, confusion, oxygenation, arterial pH; SCAP: severe community-acquired pneumonia; REA-ICU: risk of early admission to ICU; CAP-PIRO: community-acquired pneumonia-predisposition, insult, response, organ dysfunction; NA: not applicable. [#]: AUC shown indicates the range of reported studies or; [¶]: values from a meta-analysis of existing studies [41].

and specificity [29]. Elderly patients with multiple comorbid conditions are the group of patients with highest mortality in CAP [49]. Many of these patients are not considered for a higher level of care on admission [50]. These data may explain why less than 20% of patients in the highest PSI

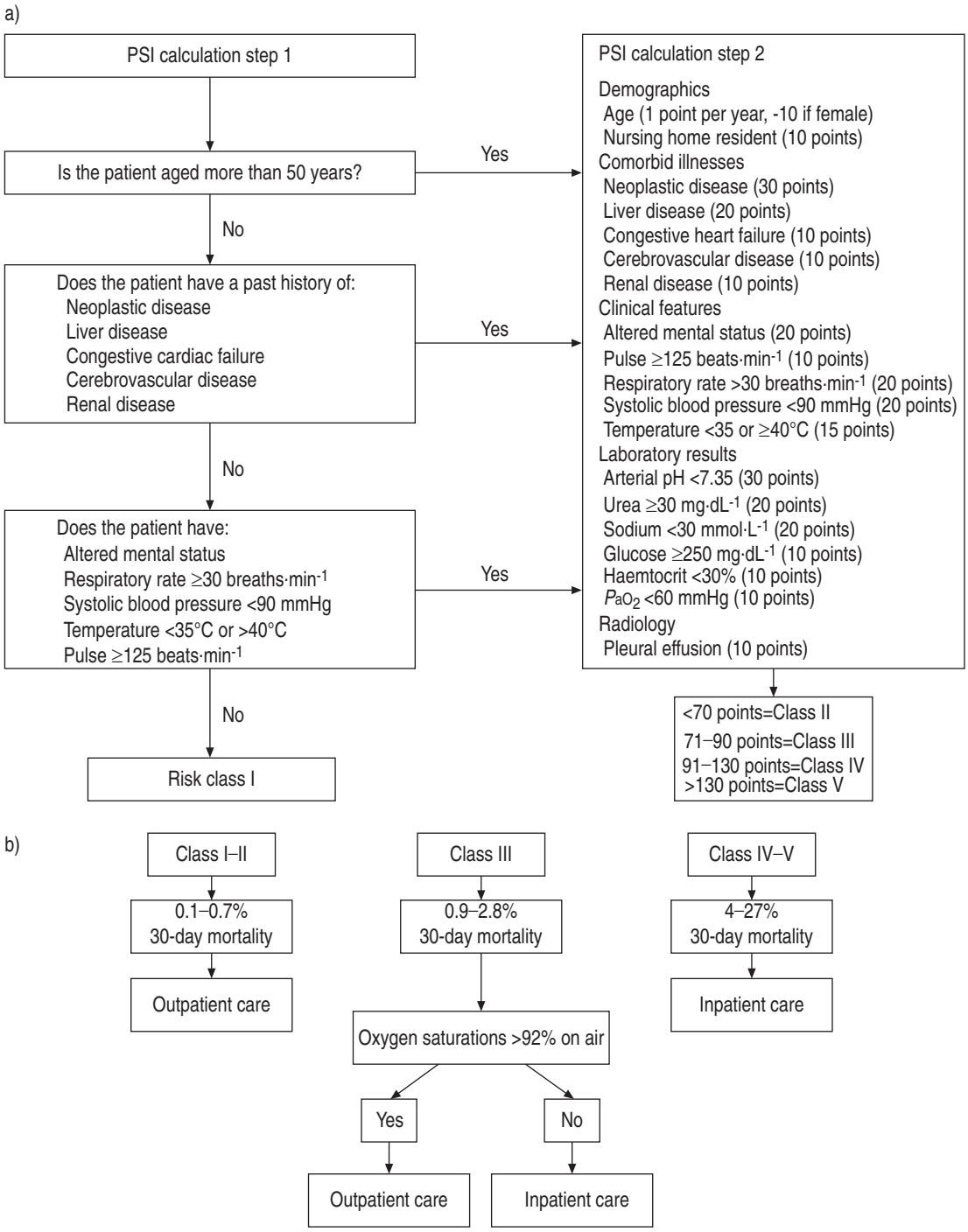

Figure 2. A clinical protocol showing a) the calculation and b) application of the Pneumonia Severity Index (PSI). P_{aO_2}: arterial oxygen tension.

class (V) require ICU admission, showing evidence of its limited value for the critical care community [51]. Furthermore, PSI does not include two of the most frequent comorbid conditions in the elderly, chronic obstructive pulmonary disease (COPD) and diabetes [52, 53]. Therefore, the PSI is a very robust tool for identifying low-risk patients suitable for discharge but should not be used to identify high-risk patients or to guide ICU care.

CURB65

CURB65 is a less complex clinical score than PSI as it uses only five variables: confusion, urea, respiratory rate, blood pressure and age older than 65 years. It was developed as a modification of the original British Thoracic Society score CURB, to which age greater than or equal to 65 years was added as a risk factor in 2003 by LIM *et al.* [11]. As with PSI, CURB65 was developed to predict 30-day mortality risk. It has been recommended by the British Thoracic Society guidelines since 2004 and is also recommended by the IDSA/ATS guidelines for CAP [9, 22].

A recommended protocol based on the CURB65 score is shown in figure 3. CURB65 is equivalent in overall predictive value to the PSI, although it may identify a smaller proportion of patients as low risk [41]. As with the PSI, CURB65 performs poorly for prediction of ICU admission [29, 54]. Other important limitations are that it does not include hypoxaemia and the dependence on laboratory testing to determine urea levels. Evidence suggests that a large proportion of "low-risk" patients using the CURB65 score still require hospitalisation, due to the presence of other markers of severity not captured by the score such as hypoxaemia, electrolyte disturbances or inability to take oral medications [55, 56]. Therefore, the CURB65 score should not be used as the sole criteria for hospitalisation decisions and should always be used with clinical judgement.

The CRB65 (confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, blood pressure $<$90 mmHg (systolic) or $\leqslant$60 mmHg (diastolic), age $\geqslant$65 years) score, without requirement to measure blood urea, is a simplified version of the score recommended initially for use in primary care to identify patients requiring hospitalisation [22]. Subsequent studies suggest that the score performs similarly to PSI and CURB65 [41]. This is important, as clinicians are more likely to remember and use simple scores, and this score appears to stratify mortality risk very well, despite being composed of only four variables [57]. It has similar limitations to the CURB65. In addition, despite originally being developed for use in the community, there is little evidence that CRB65 identifies the need for hospitalisation in this setting and one study suggests that primary care physicians rarely use or calculate the score or the variables from which it is calculated [58, 59].

A recent meta-analysis showed no significant differences in overall test performance between PSI, CURB65 and CRB65 for predicting mortality from CAP [41]. Although PSI score was the most

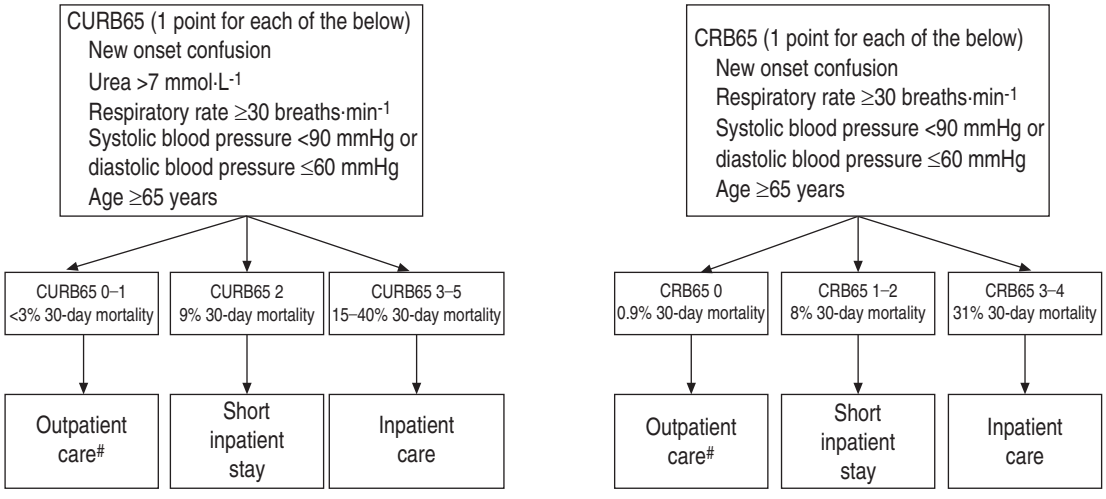

Figure 3. A clinical protocol showing the calculation and application of the CURB65 (confusion, urea $>$7 mmol·L^{-1}, respiratory rate $\geqslant$30 breaths·min^{-1}, blood pressure $<$90 mmHg (systolic) or $\leqslant$60 mmHg (diastolic), age $\geqslant$65 years) and CRB65 (confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, blood pressure $<$90 mmHg (systolic) or $\leqslant$60 mmHg (diastolic), age $\geqslant$65 years) indices. #: consider additional predictors of severity: comorbidities, hypoxia, acidosis, multilobar chest radiography involvement, severe metabolic or electrolyte disturbance, inability to take oral medications, and social factors requiring hospitalisation.

sensitive, this meta-analysis found that CURB65 and CRB65 are more specific with a higher positive predictive value, suggesting these scores may be better at identifying patients at higher risk of mortality, while PSI is a little better at identifying low-risk patients.

An important limitation of all severity scores, particularly affecting the CURB65 because of the low number of variables, is the dichotomising of variables used in the score. For example, a 64 year-old patient with a respiratory rate of 29 breaths·min^{-1} and a blood pressure of 100/61 mmHg meets none of the CURB65 criteria, but could easily have a score of 3 and "severe CAP". Overcoming this problem, JONES *et al.* [60] developed a continuous version of the CURB65 adapted for electronic devices or electronic medical record systems. By taking away this "threshold effect", this study showed that the CURB65 could be significantly improved in its ability to predict 30-day mortality [60]. Although this adds an element of complexity to the score, it has been principally designed to be used with electronic decision support systems. This is an interesting area for future research as electronic medical records systems will increasingly become the norm.

IDSA/ATS 2007 score

In their most recent 2007 guidelines the IDSA/ATS proposed different major and minor criteria to identify patients with severe CAP requiring ICU admission [9]. The major criteria are the need for mechanical ventilation and vasopressor support. The minor criteria consist of a number of physiological variables known to be associated with poor outcome (fig. 4). The presence of any one of the major criteria or three or more minor criteria is considered severe CAP and ICU care is recommended. The major criteria are not strictly speaking a predictive tool, since in most countries mechanical ventilation and vasopressor support are always provided in an ICU environment in any event [61]. However, the minor criteria are a very useful guide for identifying severe CAP [62]. A recent meta-analysis analysed the prediction of ICU admission among IDSA/ATS criteria, PSI, CURB65 and CRB65 and identified the IDSA/ATS 2007 score as the best predictor of ICU admission with a sensitivity of 65% using a cut-off of three minor criteria or more to define severe CAP [29]. A protocol based on the IDSA/ATS 2007 guidelines is shown in figure 4.

The minor criteria also perform very well to identify patients at risk of 30-day mortality. In one validation study from the UK, the minor criteria were equally predictive of mortality compared with the PSI and CURB65 scores while being superior for predicting ICU admission [63]. This study excluded patients with do not attempt resuscitation orders and studies that have included these patients find that the CURB65 and PSI scores are superior for mortality prediction [62]. This may reflect the difference between pneumonia related and unrelated deaths as described previously [25]. PSI and CURB65 seem to perform well to identify these deaths because of their dependency

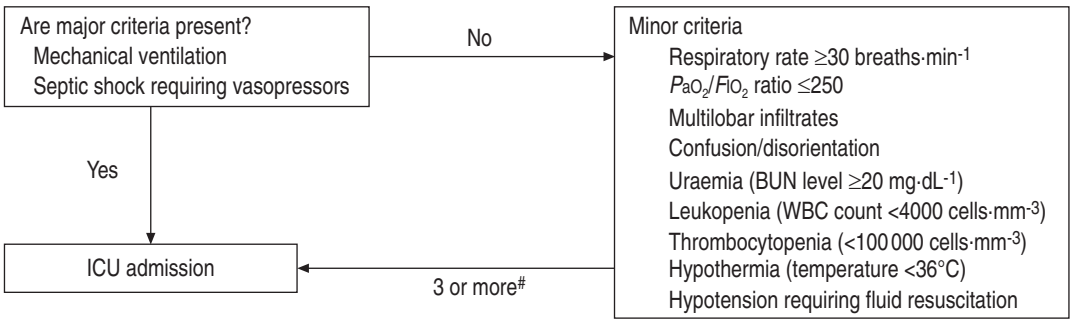

Figure 4. The Infectious Diseases Society of America/American Thoracic Society 2007 criteria for severe community-acquired pneumonia. ICU: intensive care unit; P_{aO_2}: arterial oxygen tension; F_{iO_2}: inspiratory oxygen fraction; BUN: blood urea nitrogen; WBC: white blood cell. #: Although the guidelines recommend ICU admission for patients with three or more minor criteria, not all such patients require ICU admission and these criteria should be used alongside clinical judgement.

on age and comorbidity, while the IDSA/ATS 2007 criteria are most useful to identify patients with severe CAP and, therefore, CAP-related deaths.

As with all scoring systems, the IDSA/ATS criteria have limitations. It is not 100% sensitive and some patients with severe disease without these minor criteria may still deteriorate and require higher levels of care [64, 65]. There is, as yet, no impact data showing that using these criteria improves clinical practice. In addition, the guidelines recommend ICU care for patients with three or more minor criteria, but since up to 30% of CAP patients may meet these criteria, ICU resources are likely to be insufficient to permit hospitalising this number of patients in the ICU and a more discriminatory approach is likely to be needed [66, 67]. The IDSA/ATS 2007 guidelines will shortly be updated and a number of authors have suggested modifications to improve the criteria. A retrospective study has recently found that adding arterial pH $<$7.30 as a new major criteria to the IDSA/ATS 2007 score significantly improves the sensitivity and area under the receiver operator characteristic curve (AUC) to identify patients who will require ICU care [65]. A meta-analysis of all published validation data (n=6240) found that the score could be simplified and improved by removing rare predictors (thrombocytopenia, hypothermia and leukopenia) and by adding acidosis. This modification made the score significantly simpler while improving the AUC [68]. The AUC is a well-recognised method of assessing the value of predictive tests by plotting the true positive rate against the false positive rate. Tests of no clinical value give an AUC of 0.50. Values of greater than 0.75 are generally required for a test to be considered clinically useful.

SMART-COP

The SMART-COP (systolic blood pressure, multilobar chest radiograph involvement, albumin, respiratory rate, tachycardia, confusion, oxygenation, arterial pH) is a new scoring system developed by CHARLES *et al.* [13] in 2008 in order to predict the requirement for intensive respiratory and vasopressor support. It evaluates eight parameters obtained from physical examination and laboratory testing and imaging: low systolic blood pressure (2 point), multilobar chest radiography involvement (1 point), low albumin level (1 point), high respiratory rate (1 point), tachycardia (1 point), confusion (1 point), poor oxygenation (age adjusted, 2 points) and low arterial pH (2 points) (fig. 5). The presence of three or more points identified up to 90% of patients who will received intensive respiratory care or vasopressor support [13]. Furthermore, the score identified 84% of patients who did not need intensive care initially [13]. It has been shown to be superior to CURB65 and PSI for ICU admission and equivalent for 30-day mortality prediction in some studies [63, 69]. It appears to be particularly useful in young adults because it is based on physiological derangement rather than age and comorbidities [69].

Like the IDSA/ATS criteria, the score is not perfect and a proportion of patients ultimately requiring ICU admission are not identified. So far, this score appears to have no advantage over the IDSA/ATS 2007 criteria while being slightly more complex and difficult to calculate. There are also no data on whether using this score in clinical practice improves patient outcomes. However, such data may soon be available as the Australian CAP guidelines now recommend these criteria for clinical use, guiding both triage and antibiotic selection decisions. As with all scores to predict ICU admission, the ICU admission criteria vary dramatically between different healthcare systems [29, 30] and so identifying the most useful score is interpreted in a local context.

Severe CAP score or España rule

The España rule (also referred to as the SCAP (severe CAP) score or CURXO80 (confusion, urea $>$30 mg·dL^{-1}, respiratory rate $>$30 breaths·min^{-1}, X-ray multilobar infiltrates, oxygenation: arterial oxygen tension/inspiratory oxygen fraction ratio $<$250, and age $\geq$80 years) is another prediction tool developed in 2006 by ESPAÑA *et al.* [14]. Again, it was designed to identify patients with CAP who require intensive respiratory care or vasopressor support [14]. The score includes eight clinical variables and it is divided in two major criteria and six minor criteria. The two major

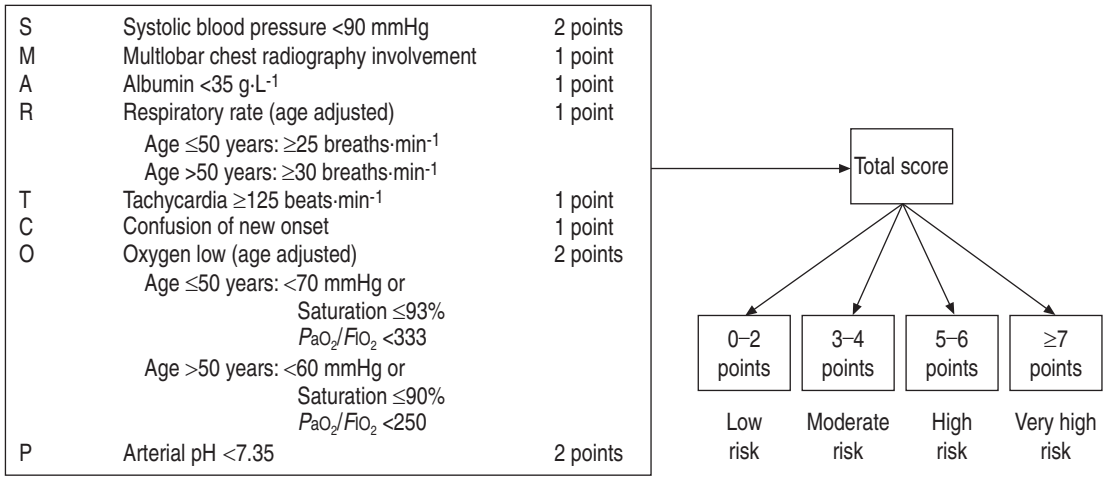

Figure 5. Calculation and clinical use of the SMART-COP rule for severe community-acquired pneumonia. P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction.

criteria are acidosis (pH) and low systolic blood pressure. The six minor criteria are confusion, uraemia, elevated respiratory rate, multilobar/bilateral lung infiltrates, low arterial oxygen and age. The presence of one major criterion or two or more minor criteria predicts severe CAP.

Based on in-hospital mortality, need for ICU admission and the need for mechanical ventilation and/or vasopressor support, a comparative evaluation [14] has shown SCAP to be superior to CURB65, but similar to PSI for prediction of severe CAP. However, in a validation of the different severity CAP scores, BROWN *et al.* [67] detected that patients with SCAP criteria had similar 30-day mortality but longer length of hospital stay when compared with severe CAP identified using the IDSA/ATS 2007 score. In this study, the IDSA/ATS 2007 criteria achieved better results than SCAP based only on the need for ICU [67].

The score does not appear to have major advantages over the IDSA/ATS 2007 criteria and has limited external validation data to support its use. In particular, there is no evidence that it improves patient outcome when implemented in clinical practice.

Other scores

There are multiple additional scoring systems that have been developed for CAP, but in most cases these scores have limited external validation or are not widely recognised or used.

Examples are the risk of early admission to ICU index (REA-ICU), which was developed to identify patients at risk of early deterioration and ICU admission [16], and the CORB index, which is a modification of the CURB65 score to include oxygenation [17]. There are, as yet, limited data to suggest these scores are an advance on the more recognised scores described above and so they will not be discussed further in this chapter.

A single score has been described to predict outcome in patients with CAP admitted to the ICU. The CAP-PIRO score is based on eight variables using the PIRO (predisposition, insult, response and organ dysfunction) concept suggested for prediction of risk for sepsis [15]. The variables in this CAP score are: comorbidities such as COPD or immunocompromised (1 point), age greater than 70 years (1 point), bacteraemia (1 point), multilobar infiltrates (1 point), shock (1 point), severe hypoxaemia (1 point), acute respiratory distress syndrome (1 point) and acute renal failure (1 point). It classifies patients into four risk categories: low (0–2 points), mild (3 points), high (4 points) and very high (5–8 points). In a cohort of 529 ICU patients admitted with CAP, this score was able to significantly predict 28-day ICU mortality, with a better performance than the IDSA/ATS criteria or another ICU score, the APACHE (acute physiology and chronic health

evaluation) II index [15]. Again, more broad independent validation is needed to justify the use of a CAP specific prediction tool for ICU admitted patients; however, studies in the ICU have consistently shown that CAP specific scoring systems outperform generic tools such as APACHE or generic sepsis tools [70].

Scoring systems have been investigated in other subgroups of CAP, such as healthcare-associated pneumonia, but there is limited data available.

The strengths, weaknesses, clinical indications and summary predictive characteristics of the most widely recognised scoring systems for CAP are shown in table 1.

Biomarkers

The lack of a perfect clinical scoring system to predict severity of illness has promoted several studies with biomarkers in recent years to predict severity of CAP. Patients with CAP in the hospital setting exhibit markedly abnormal levels of various biomarkers of infection, inflammation and coagulation [71]. Therefore, changes in biomarker levels on CAP admission and during the course of the disease may enable physicians to identify those patients who are most at risk for deterioration and progression toward severe illness. At present, the combination of biomarkers and clinical scores has shown promising results in predicting mortality and severe outcomes in CAP [71]. The most relevant and extensively studied biomarkers studied in severe CAP are shown in table 2.

Procalcitonin

Procalcitonin (PCT) is a calcitonin precursor peptide that increases during inflammatory and infectious diseases. PCT concentrations in the serum of healthy subjects are undetectable or low (less than 0.1 $ng \cdot mL^{-1}$) and the synthesis of this molecule is particularly induced during severe bacterial infection, sepsis and multiple organ dysfunction syndrome [72]. PCT is one of the most widely researched biomarkers and is also used clinically in CAP in some countries.

PCT has predominantly been evaluated as a diagnostic test for infections, distinguishing bacterial from viral infections and for guiding the need for antibiotic therapy [71–75]. Low levels of PCT are associated with an excellent prognosis and in randomised controlled trials have been shown to identify patients who may not require antibiotic therapy, or require a shorter course of treatment [76, 77]. PCT again illustrates the difficulties of extrapolating good prediction in a large population to making decisions for individuals, because although across these large cohorts PCT performed well, many individuals with low PCT levels still required antibiotics and some had poor outcomes. This emphasises again that no biomarker or prediction tool can be used as the sole guide for clinical decisions at the individual patient level.

For predicting prognosis, the results of studies into PCT have given conflicting results. Several studies have shown that PCT is superior to C-reactive protein for mortality prediction [74, 75], while others have shown the two are equivalent [70]. The AUC for mortality prediction has been reported to be good, and equivalent to CRB65 in some studies [74]. It was, however, quite poor at 0.60 in the largest and highest quality study to evaluate PCT, the ProHOSP

Table 2. Biomarkers associated with severe community-acquired pneumonia

Procalcitonin
C-reactive protein
Proadrenomedullin
D-dimer
Brain natriuretic peptide
Copeptin
Pro-endothelin 1
White blood cell count
Others
Cortisol
Midregional proatrial natriuretic peptide
Genomic bacterial load
Pro-atrial natriuretic peptide
Inflammatory cytokines (IL-6, TNF-α)
Prothrombin fragment 1.2
Thrombin–antithrombin complex
Fibrinogen

IL: interleukin; TNF: tumour necrosis factor.

(procalcitonin-guided antibiotic therapy and hospitalisation in patients with lower respiratory tract infection (LRTI)) randomised controlled trial [76]. This was similar to another large study of over 1600 patients, the GenIMS (Genetic and Inflammatory Markers of Sepsis Study) cohort, which also found an area of the curve of 0.65 [78]. Most studies, including the ProHOSP trial, have demonstrated that PCT has additional prognostic value over and above CURB65 and PSI. Overall it appears PCT is not useful alone as a prognostic marker, but the combination of clinical scores and biomarkers may be a very promising approach [71].

C-reactive protein

C-reactive protein (CRP) is an acute phase protein produced in the liver and is stimulated by inflammatory cytokines. Although it was the first acute phase protein to be described [79] and it is commonly used in clinical practice, the use of CRP in the assessment of severe CAP has not consistently shown positive results. Small observational studies suggested that an elevated CRP level is relatively nonspecific and is not directly related to severity [80, 81]. However, other studies described a good correlation between CRP levels with the prediction of mortality and the decision of site of care [71, 82, 83]. Different studies showed that when CRP is added to clinical scores such as PSI and CURB65, the predictive severity accuracy is higher [71, 84]. In addition, MENÉNDEZ *et al.* [71] conducted a prospective cohort study investigating whether information about different biomarker levels on admission may increase the accuracy of clinical prognostic scales to predict 30-mortality in CAP. The reported AUC for mortality prediction by CRP alone varies from 0.50 to 0.70 and is inconsistent between studies. Therefore, use of this marker alone to determine severity is not recommended, but adding CRP to clinical scores or a panel of biomarkers may be a useful future approach. CRP appears to be most useful to monitor response to treatment, with a reduction of 50% or more by day 3 or day 4 of admission being an excellent marker of prognosis [71, 84]. A major advantage of biomarkers generally is their ability to monitor response to treatment.

Proadrenomedullin

Proadrenomedullin (pro-ADM) is a peptide expressed at high levels in vascular endothelium, and is also expressed in the adrenal medulla, the heart, kidneys and lungs. pro-ADM causes vasodilatation, immune modulation and bactericidal activity [85] and at very high levels may contribute to the pathophysiology of septic shock, causing hypotension. It is difficult to measure owing to its rapid circulation clearance [86–88]. Different studies in CAP have shown good correlation between pro-ADM levels and severity and short-term mortality [89, 90]. In the previously described ProHOSP trial, the AUC for pro-ADM to predict mortality was 0.72, which was superior in this study to CURB65 and PSI [90]. In addition, when it is combined with PSI and CURB65, pro-ADM may improve the prediction of mortality and complications of CAP.

Recent studies have been focused on a fragment of pro-ADM, which is more stable than the full-length proADM, known as midregional pro-ADM. Some studies have been carried to determine its prognostic value with promising results in CAP and sepsis [89–92]. BELLO *et al.* [92] recently confirmed these results in a prospective cohort study where midregional proADM levels had high short- and long-term prognostic accuracy, increasing the accuracy of different clinical scores such as PSI and CURB65.

The adrenomedullin based biomarkers require validation in further cohorts and the optimal cut-offs for clinical management decisions have yet to be determined, but it appears a promising marker.

D-dimer

D-dimer is a protein released into the blood during dissolution of a fibrin clot. Increased plasma levels of D-dimer have been detected in patients with severe sepsis, disseminated intravascular coagulation, thrombotic events, hepatic diseases, surgery and trauma [93, 94]. In CAP,

SHILTON *et al.* [95] demonstrated a positive correlation between D-dimer levels and PSI and hospital mortality. In addition, QUEROL-RIBELLES *et al.* [96] investigated the relationship between plasma D-dimer levels and the prognostic variables included in PSI. These authors found a good relationship between D-dimer levels and PSI, radiological pneumonia extension and 30-day mortality risk [96]. Other studies correlated high plasma D-dimer levels with higher mortality in severely ill patients admitted to the ICU [97], and have related this biomarker to important outcomes such as 30-day mortality and the need for mechanical ventilation or vasopressor support [96, 98, 99]. CHALMERS *et al.* [98] and SNIJDERS *et al.* [100] both demonstrated that admission D-dimer may identify patients with low risk of death and major complications. The reported AUC has varied from 0.71 to 0.78. Although highly promising, D-dimer has not been evaluated in large cohorts to the extent that the other markers have, and further validation is needed.

Brain natriuretic peptide

Proteins of the family of natriuretic peptides, such as brain natriuretic peptide (BNP), are established biomarkers for congestive heart failure [101]. Trigger factors such as proinflammatory cytokines and the sympathetic nervous system have been identified to induce the release of BNP [102]. The presence of heart failure, renal dysfunction and the release of proinflammatory cytokines may elevate BNP levels [103]. One pilot study in CAP hospitalised patients showed that BNP was significantly higher in patients dying within 30 days, and the AUC using BNP to predict death was higher than that of the PSI [104]. These findings were confirmed in a prospective observational study conducted by CHRIST-CRAIN *et al.* [105]. In this study, the authors found that BNP levels were significantly higher in nonsurvivors compared with survivors. In addition, the AUC for prediction of survival was comparable to the AUC of the PSI, and the combination of BNP and the PSI significantly improved the prognostic accuracy of the PSI alone [88]. However, recent studies in sepsis suggested a possible false elevation of BNP due to a decreased clearance [106]. As with other biomarkers, there is a need for further validation and clinical correlation.

Copeptin

Copeptin is a glycopeptide that plays an important role in the structural formation of vasopressin, a hormone produced by the hypothalamus that is stimulated by hypotension, hypoxia, acidosis and infections [107]. Elevated levels of vasopressin have been commonly associated with a response to early septic shock. However, the difficulties in measuring circulating levels of vasopressin have opened the door to exploration of other similar biomarkers such as copeptin. MÜLLER *et al.* [108] described, in 2007, its promising role as a novel biomarker in LRTIs. In this study, patients with LRTI had significantly higher levels of copeptin as compared to controls, with the highest levels in those patients with CAP. In addition, copeptin levels on admission in patients who died were significantly higher as compared to levels in survivors [108]. The AUC for survival for copeptin was similar to PCT and higher than CRP and leukocyte count [108]. In the CAPNETZ (German Competence Network for Community-Acquired Pneumonia) study, copeptin was detected as the best biomarker for the risk stratification of CAP patients [109]. In this study, copeptin values were significantly lower in CAP survivors and correlated with the severity of disease measured by CRB65 [109].

Other biomarkers

Elevated levels of a wide range of biomarkers have been reported in small to medium sized studies, including white blood cell count [10], cortisol [110], pro-endothelin 1 [111], cytokines [112], natriuretic peptides [113], lactate and cardiac troponins. This list is growing rapidly but the true measure of the value of these markers will be their ability to influence clinical practice in the future.

Microbiological markers of severity

To date, and throughout this chapter, the predictors of severity discussed have been exclusively focused on the host response to infection. However, CAP represents the interface between the host response and the infecting organism. It is likely that the infecting pathogen has a major impact on prognosis but, to date, microbiological testing in CAP is so unreliable as to make this of little clinical value. This may be changing, as a recent initial report by RELLO *et al.* [114] showed that quantitative DNA load of *Streptococcus pneumoniae* in blood correlated with mortality and the presence of septic shock and mechanical ventilation. This has now been confirmed by a number of groups and also demonstrated for other bacterial pathogens [115, 116]. It is hoped that as technology develops, rapid microbial diagnosis and assessment of microbial load will become an adjunct to clinical severity assessment.

Conclusions

The early identification of patients at risk of serious complications is critical to the management of CAP. Prediction tools have made a major contribution to CAP management over the past 15 years and have entered all of the major national and international guidelines. While a number of scores now show good prediction of CAP related outcomes, intervention studies demonstrating that use of these scores in clinical practice can improve patient outcomes are now needed.

Scoring systems are developing and new tools should ideally predict 30-day mortality and the requirement for mechanical ventilation and vasopressor support. Most importantly, scores should identify those patient groups with preventable deterioration to target new and existing therapies to improve patient outcomes.

Statement of Interest

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References

1. Marston BJ, Plouffe JF, File TM Jr, *et al.* Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance study in Ohio. The Community-Based Pneumonia Incidence Study Group. *Arch Intern Med* 1997; 157: 1709–1718.
2. Akram AR, Chalmers JD, Hill AT. Predicting mortality with severity assessment tools in out-patients with community-acquired pneumonia. *QJM* 2011; 104: 871–879.
3. Angus DC, Marrie TJ, Obrosky DS, *et al.* Severe community-acquired pneumonia: use of intensive care services and evaluation of American and British Thoracic Society Diagnostic criteria. *Am J Respir Crit Care Med* 2002; 166: 717–723.
4. Rodríguez A, Mendia A, Sirvent JM, *et al.* Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. *Crit Care Med* 2007; 35: 1493–1498.
5. Restrepo MI, Anzueto A. Severe community-acquired pneumonia. *Infect Dis Clin North Am* 2009; 23: 503–520.
6. Woodhead M, Welch CA, Harrison DA, *et al.* Community-acquired pneumonia on the intensive care unit: secondary analysis of 17,869 cases in the ICNARC Case Mix Programme Database. *Crit Care* 2006; 10: Suppl. 2, S1.
7. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax* 2012; 67: 71–79.
8. Fine MJ, Auble TE, Yealy DM, *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336: 243–250.
9. Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44: Suppl. 2, S27–S72.
10. Lim WS, Lewis S, Macfarlane JT. Severity prediction rules in community acquired pneumonia: a validation study. *Thorax* 2000; 55: 219–223.
11. Lim WS, van der Eerden MM, Laing R, *et al.* Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003; 58: 377–382.

12. Niederman MS, Mandell LA, Anzueto A, *et al.* Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001; 163: 1730–1754.
13. Charles PG, Wolfe R, Whitby M, *et al.* SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. *Clin Infect Dis* 2008; 47: 375–384.
14. España PP, Capelastegui A, Gorordo I, *et al.* Development and validation of a clinical prediction rule for severe community-acquired pneumonia. *Am J Respir Crit Care Med* 2006; 174: 1249–1256.
15. Rello J, Rodriguez A, Lisboa T, *et al.* PIRO score for community-acquired pneumonia: a new prediction rule for assessment of severity in intensive care unit patients with community-acquired pneumonia. *Crit Care Med* 2009; 37: 456–462.
16. Renaud B, Labarère J, Coma E, *et al.* Risk stratification of early admission to the intensive care unit of patients with no major criteria of severe community-acquired pneumonia: development of an international prediction rule. *Crit Care* 2009; 13: R54.
17. Buising KL, Thursky KA, Black JF, *et al.* Identifying severe community-acquired pneumonia in the emergency department: a simple clinical prediction tool. *Emerg Med Australas* 2007; 19: 418–426.
18. Chalmers JD, Singanayagam A, Akram AR, *et al.* Safety and efficacy of CURB65-guided antibiotic therapy in community-acquired pneumonia. *J Antimicrob Chemother* 2011; 66: 416–423.
19. Capelastegui A, España PP, Quintana JM, *et al.* Development of a prognostic index for 90-day mortality in patients discharged after admission to hospital for community-acquired pneumonia. *Thorax* 2009; 64: 496–501.
20. Chalmers JD, Singanayagam A, Murray MP, *et al.* Risk factors for complicated parapneumonic effusion and empyema on presentation to hospital with community-acquired pneumonia. *Thorax* 2009; 64: 592–597.
21. Falguera M, Trujillano J, Caro S, *et al.* A prediction rule for estimating the risk of bacteremia in patients with community-acquired pneumonia. *Clin Infect Dis* 2009; 49: 409–416.
22. Lim WS, Baudouin SV, George RC, *et al.* BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; 64: Suppl. 3, iii1–iii55.
23. Sibila O, Restrepo MI, Anzueto A. What is the best antimicrobial treatment for severe community-acquired pneumonia (including the role of steroids and statins and other immunomodulatory agents). *Infect Dis Clin North Am* 2013; 27: 133–147.
24. Buising KL, Thursky KA, Black JF, *et al.* A prospective comparison of severity scores for identifying patients with severe community acquired pneumonia: reconsidering what is meant by severe pneumonia. *Thorax* 2006; 61: 419–424.
25. Mortensen EM, Coley CM, Singer DE, *et al.* Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Arch Intern Med* 2002; 162: 1059–1064.
26. Bauer TT, Welte T, Strauss R, *et al.* Why do nonsurvivors from community-acquired pneumonia not receive ventilatory support? *Lung* 2013; 191: 417–424.
27. Marrie TJ, Fine MJ, Kapoor WN, *et al.* Community-acquired pneumonia and do not resuscitate orders. *J Am Geriatr Soc* 2002; 50: 290–299.
28. Chalmers JD. ICU admission and severity assessment in community-acquired pneumonia. *Crit Care* 2009; 13: 156.
29. Chalmers JD, Mandal P, Singanayagam A, *et al.* Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. *Intensive Care Med* 2011; 37: 1409–1420.
30. Wunsch H, Angus DC, Harrison DA, *et al.* Comparison of medical admissions to intensive care units in the United States and United Kingdom. *Am J Respir Crit Care Med* 2011; 183: 1666–1673.
31. Restrepo MI, Mortensen EM, Rello J, *et al.* Late admission to the ICU in patients with community-acquired pneumonia is associated with higher mortality. *Chest* 2010; 137: 552–557.
32. Renaud B, Santin A, Coma E, *et al.* Association between timing of intensive care unit admission and outcomes for emergency department patients with community-acquired pneumonia. *Crit Care Med* 2009; 37: 2867–2874.
33. Simpson JC, Macfarlane JT, Watson J, *et al.* A national confidential enquiry into community acquired pneumonia deaths in young adults in England and Wales. British Thoracic Society Research Committee and Public Health Laboratory Service. *Thorax* 2000; 55: 1040–1045.
34. Cillóniz C, Ewig S, Polverino E, *et al.* Microbial aetiology of community-acquired pneumonia and its relation to severity. *Thorax* 2011; 66: 340–346.
35. Singanayagam A, Chalmers JD. Severity assessment scores to guide empirical use of antibiotics in community acquired pneumonia. *Lancet Respir Med* 2013; 1: 653–662.
36. Alfrageme I, Aspa J, Bello S, *et al.* Normativas para el diagnostico y el tratamiento de la neumonia adquirida en la comunidad. Sociedad Espanola de Neumologia y Cirugia Toracica (SEPAR) [Guidelines for the diagnosis and management of community-acquired Pneumonia. Spanish Sociaty of Pulmonology and Thoracic surgery (SEPAR)]. *Arch Bronconeumol* 2005; 41: 272–289.
37. Working Group of the South African Thoracic Society. Management of community-acquired pneumonia in adults. *S Afr Med J* 2007; 97: 1296–1306.
38. Tang CM, Macfarlane JT. Early management of younger adults dying of community-acquired pneumonia. *Respir Med* 1993; 87: 289–294.
39. Neill AM, Martin IR, Weir R, *et al.* Community-acquired pneumonia: aetiology and usefulness of severity criteria on admission. *Thorax* 1996; 51: 1010–1016.

40. Singanayagam A, Chalmers JD, Hill AT. Severity assessment in community-acquired pneumonia. *QJM* 2009; 102: 379–388.
41. Chalmers JD, Singanayagam A, Akram AR, *et al.* Severity assessment tools for predicting mortality in hospitalised patients with community-acquired pneumonia. Systematic review and meta-analysis. *Thorax* 2010; 65: 878–883.
42. Chalmers JD, Akram AR, Hill AT. Increasing outpatient treatment of mild community-acquired pneumonia: systematic review and meta-analysis. *Eur Respir J* 2011; 37: 858–864.
43. Atlas SJ, Benzer TI, Borowsky LH, *et al.* Safely increasing the proportion of patients with community-acquired pneumonia treated as outpatients: an interventional trial. *Arch Intern Med* 1998; 158: 1350–1356.
44. Marrie TJ, Lau CY, Wheeler SL, *et al.* A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. *JAMA* 2000; 283: 749–755.
45. Carratalà J, Fernández-Sabé N, Ortega L, *et al.* Outpatient care compared with hospitalization for community-acquired pneumonia: a randomized trial in low-risk patients. *Ann Intern Med* 2005; 142: 165–172.
46. Renaud B, Coma E, Labarere J, *et al.* Routine use of the Pneumonia Severity Index for guiding the site-of-treatment decision of patients with pneumonia in the emergency department: a multicenter, prospective, observational, controlled cohort study. *Clin Infect Dis* 2007; 44: 41–49.
47. Yealy DM, Auble TE, Stone RA, *et al.* Effect of increasing the intensity of implementing pneumonia guidelines: a randomised controlled trial. *Ann Intern Med* 2005; 143: 881–894.
48. Lee RW, Lindstrom ST. A teaching hospital's experience applying the Pneumonia Severity Index and antibiotic guidelines in the management of community-acquired pneumonia. *Respirology* 2007; 12: 754–758.
49. Kaplan V, Angus DC, Griffin MF, *et al.* Hospitalized community-acquired pneumonia in the elderly: age- and sex-related patterns of care and outcome in the United States. *Am J Respir Crit Care Med* 2002; 165: 766–772.
50. Ewig S, Birkner N, Strauss R, *et al.* New perspectives on community-acquired pneumonia in 388 406 patients. Results from a nationwide mandatory performance measurement programme in healthcare quality. *Thorax* 2009; 64: 1062–1069.
51. Valencia M, Badia JR, Cavalcanti M, *et al.* Pneumonia severity index class V patients with community-acquired pneumonia: characteristics, outcomes and value of severity scores. *Chest* 2007; 132: 515–522.
52. Restrepo MI, Mortensen EM, Pugh JA, *et al.* COPD is associated with increased mortality in patients with community-acquired pneumonia. *Eur Respir J* 2006; 28: 346–351.
53. Yende S, van der Poll T, Lee M, *et al.* The influence of pre-existing diabetes mellitus on the host immune response and outcome of pneumonia: analysis of two multicentre cohort studies. *Thorax* 2010; 65: 870–877.
54. Man SY, Lee N, Ip M, *et al.* Prospective comparison of three predictive rules for assessing severity of community-acquired pneumonia in Hong Kong. *Thorax* 2007; 62: 348–353.
55. Choudhury G, Chalmers JD, Mandal P, *et al.* Physician judgement is a crucial adjunct to pneumonia severity scores in low-risk patients. *Eur Respir J* 2011; 38: 643–648.
56. Aliberti S, Ramirez J, Cosentini R, *et al.* Low CURB-65 is of limited value in deciding discharge of patients with community-acquired pneumonia. *Respir Med* 2011; 105: 1732–1738.
57. Ewig S, Welte T. CRB-65 for the assessment of pneumonia severity: who could ask for more? *Thorax* 2008; 63: 665–666.
58. Bont J, Hak E, Hoes AW, *et al.* Predicting death in elderly patients with community-acquired pneumonia: a prospective validation study reevaluating the CRB-65 severity assessment tool. *Arch Intern Med* 2008; 168: 1465–1468.
59. Francis NA, Cals JW, Butler CC, *et al.* Severity assessment for lower respiratory tract infections: potential use and validity of the CRB-65 in primary care. *Prim Care Respir J* 2012; 21: 65–70.
60. Jones BE, Jones J, Bewick T, *et al.* CURB-65 pneumonia severity assessment adapted for electronic decision support. *Chest* 2011; 140: 156–163.
61. Charles PG, Davis JS, Grayson ML. Rocket science and the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines for severe community-acquired pneumonia. *Clin Infect Dis* 2009; 48: 1796.
62. Phua J, See KC, Chan YH, *et al.* Validation and clinical implications of the IDSA/ATS minor criteria for severe community-acquired pneumonia. *Thorax* 2009; 64: 598–603.
63. Chalmers JD, Taylor JK, Mandal P, *et al.* Validation of the Infectious Diseases Society of America/American Thoratic Society minor criteria for intensive care unit admission in community-acquired pneumonia patients without major criteria or contraindications to intensive care unit care. *Clin Infect Dis* 2011; 53: 503–511.
64. Sibila O, Mortensen EM, Redrow G, *et al.* Evaluation of the IDSA/ATS minor criteria for severe community-acquired pneumonia. *Hosp Pract (1995)* 2012; 40: 158–164.
65. Sibila O, Meduri GU, Mortensen EM, *et al.* Improving the 2007 Infectious Disease Society of America/American Thoracic Society severe community-acquired pneumonia criteria to predict intensive care unit admission. *J Crit Care* 2013; 28: 284–290.
66. Kontou P, Kuti JL, Nicolau DP. Validation of the Infectious Diseases Society of America/American Thoracic Society criteria to predict severe community-acquired pneumonia caused by *Streptococcus pneumoniae*. *Am J Emerg Med* 2009; 27: 968–974.
67. Brown SM, Jones BE, Jephson AR, *et al.* Validation of the Infectious Disease Society of America/American Thoracic Society 2007 guidelines for severe community-acquired pneumonia. *Crit Care Med* 2009; 37: 3010–3016.

68. Salih W, Schembri S, Chalmers JD. Simplification of the IDSA/ATS criteria for severe community-acquired pneumonia using meta-analysis and observational data. Eur Respir J 2013 [In press DOI: 10.1183/09031936.00089513].
69. Chalmers JD, Singanayagam A, Hill AT. Predicting the need for mechanical ventilation and/or inotropic support for young adults admitted to the hospital with community-acquired pneumonia. *Clin Infect Dis* 2008; 47: 1571–1574.
70. Barlow G, Nathwani D, Davey P. The CURB65 pneumonia severity score outperforms genetic sepsis and early waning scores in predicting mortality in community-acquired pneumonia. *Thorax* 2007; 62: 253–259.
71. Menéndez R, Martínez R, Reyes S, *et al.* Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. *Thorax* 2009; 64: 587–591.
72. Hedlund J, Hansson LO. Procalcitonin and C-reactive protein levels in community-acquired pneumonia: correlation with etiology and prognosis. *Infection* 2000; 28: 68–73.
73. Müller B, Harbarth S, Stolz D, *et al.* Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. *BMC Infect Dis* 2007; 7: 10.
74. Krüger S, Ewig S, Marre R, *et al.* Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. *Eur Respir J* 2008; 31: 349–355.
75. Huang DT, Weissfeld LA, Kellum JA, *et al.* Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. *Ann Emerg Med* 2008; 52: 48–58.
76. Schuetz P, Christ-Crain M, Thomann R, *et al.* Effect of procalcitonin-based guidelines *vs* standard guidelines on antibiotic use in lower respiratory tract infections: The ProHOSP randomized controlled trial. *JAMA* 2009; 302: 1059–1066.
77. Christ-Crain M, Stolz D, Bingisser R, *et al.* Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2006; 174: 84–93.
78. Huang DT, Angus DC, Kellum JA, *et al.* Midregional proadrenomedullin as a prognostic tool in community-acquired pneumonia. *Chest* 2009; 136: 823–831.
79. Volanakis JE, Kaplan MH. Specificity of C-reactive protein for choline phosphate residues of pneumococcal C-polysaccharide. *Proc Soc Exp Biol Med* 1971; 136: 612–614.
80. Smith RP, Lipworth BJ, Cree IA, *et al.* C-reactive protein. A clinical marker in community-acquired pneumonia. *Chest* 1995; 108: 1288–1291.
81. García Vázquez E, Martínez JA, Mensa JA, *et al.* C-reactive protein levels in community-acquired pneumonia. *Eur Respir J* 2003; 21: 702–705.
82. Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. *Am J Med* 2008; 121: 219–225.
83. Lee JH, Kim J, Kim K, *et al.* Albumin and C-reactive protein have prognostic significance in patients with community-acquired pneumonia. *J Crit Care* 2011; 26: 287–294.
84. Hohenthal U, Hurme S, Helenius H, *et al.* Utility of C-reactive protein in assessing the disease severity and complications of community-acquired pneumonia. *Clin Microbiol Infect* 2009; 15: 1026–1032.
85. Hirata Y, Mitaka C, Sato K, *et al.* Increased circulating adrenomedullin, a novel vasodilatory peptide, in sepsis. *J Clin Endocrinol Metab* 1996; 81: 1449–1453.
86. Eto T. A review of the biological properties and clinical implications of adrenomedullin and proadrenomedullin N-terminal 20 peptide (PAMP), hypotensive and vasodilating peptides. *Peptides* 2001; 22: 1693–1711.
87. Jougasaki M, Burnett JC Jr. Adrenomedullin: potential in physiology and pathophysiology. *Life Sci* 2000; 66: 855–872.
88. Kato J, Tsuruda T, Kitamura K, *et al.* Adrenomedullin: a possible autocrine or paracrine hormone in the cardiac ventricles. Hypertens Res 2003; 26: Suppl, S113–S119.
89. Christ-Crain M, Morgenthaler NG, Stolz D, *et al.* Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia. *Crit Care* 2006; 10: R96.
90. Schuetz P, Wolbers M, Christ-Crain M, *et al.* Prohormones for prediction of adverse medical outcome in community-acquired pneumonia and lower respiratory tract infections. *Crit Care* 2010; 14: R106.
91. Guignant C, Voirin N, Venet F, *et al.* Assessment of pro-vasopressin and pro-adrenomedullin as predictors of 28-day mortality in septic shock patients. *Intensive Care Med* 2009; 35: 1859–1867.
92. Bello S, Lasierrra AB, Mincholé E, *et al.* Prognostic power of proadrenomedullin in community-acquired pneumonia is independent of aetiology. *Eur Respir J* 2012; 39: 1144–1155.
93. Ginsberg JS, Wells PS, Kearon C, *et al.* Sensitivity and specificity of a rapid whole-blood assay for D-dimer in the diagnosis of pulmonary embolism. *Ann Intern Med* 1998; 129: 1006–1011.
94. Wada H, Sakuragawa N, Mori Y, *et al.* Hemostatic molecular markers before the onset of disseminated intravascular coagulation. *Am J Hematol* 1999; 60: 273–278.
95. Shilon Y, Shitrit AB, Rudensky B, *et al.* A rapid quantitative D-dimer assay at admission correlates with the severity of community acquired pneumonia. *Blood Coagul Fibrinolysis* 2003; 14: 745–748.
96. Querol-Ribelles JM, Tenias JM, Grau E, *et al.* Plasma d-dimer levels correlate with outcomes in patients with community-acquired pneumonia. *Chest* 2004; 126: 1087–1092.
97. Kollef MH, Eisenberg PR, Shannon W. A rapid assay for the detection of circulating D-dimer is associated with clinical outcomes among critically ill patients. *Crit Care Med* 1998; 26: 1054–1060.

98. Chalmers JD, Singanayagam A, Scally C, *et al.* Admission D-dimer can identify low-risk patients with community-acquired pneumonia. *Ann Emerg Med* 2009; 53: 633–638.
99. Milbrandt EB, Reade MC, Lee M, *et al.* Prevalence and significance of coagulation abnormalities in community-acquired pneumonia. *Mol Med* 2009; 15: 438–445.
100. Snijders D, Schoorl M, Schoorl M, *et al.* D-dimer levels in assessing severity and clinical outcome in patients with community-acquired pneumonia. A secondary analysis of a randomised clinical trial. *Eur J Intern Med* 2012; 23: 436–441.
101. McDonagh TA, Robb SD, Murdoch DR, *et al.* Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 1998; 351: 9–13.
102. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J* 1999; 138: 285–290.
103. Maisel AS, Krishnaswamy P, Nowak RM, *et al.* Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002; 347: 161–167.
104. Mueller C, Laule-Kilian K, Scholer A, *et al.* B-type natriuretic peptide for risk stratification in community-acquired pneumonia. *J Intern Med* 2005; 258: 391–393.
105. Christ-Crain M, Breidthardt T, Stolz D, *et al.* Use of B-type natriuretic peptide in the risk stratification of community-acquired pneumonia. *J Intern Med* 2008; 264: 166–176.
106. Pirracchio R, Deye N, Lukaszewicz AC, *et al.* Impaired plasma B-type natriuretic peptide clearance in human septic shock. *Crit Care Med* 2008; 36: 2542–2546.
107. de Bree FM, Burbach JP. Structure-function relationships of the vasopressin prohormone domains. *Cell Mol Neurobiol* 1998; 18: 173–191.
108. Müller B, Morgenthaler N, Stolz D, *et al.* Circulating levels of copeptin, a novel biomarker, in lower respiratory tract infections. *Eur J Clin Invest* 2007; 37: 145–152.
109. Krüger S, Papassotiriou J, Marre R, *et al.* Pro-atrial natriuretic peptide and pro-vasopressin to predict severity and prognosis in community-acquired pneumonia: results from the German competence network CAPNETZ. *Intensive Care Med* 2007; 33: 2069–2078.
110. Christ-Crain M, Stolz D, Jutla S, *et al.* Free and total cortisol levels as predicts of severity and outcome in community-acquired pneumonia. *Am J Respir Crit Care Med* 2007; 176: 913–920.
111. Brauner JS, Rohde LE, Clausell N. Circulating endothelin-I and tumor necrosis factor-α: early predictors of mortality in patients with septic shock. *Intensive Care Med* 2000; 26: 305–313.
112. Ramírez P, Ferrer M, Martí V, *et al.* Inflammatory biomarkers and prediction for intensive care unit admission in severe community-acquired pneumonia. *Crit Care Med* 2011; 39: 2211–2217.
113. Krüger S, Ewig S, Kunde J, *et al.* Pro-atrial natriuretic peptide and pro-vasopressin for predicting short-term and long-term mortality in community-acquired pneumonia: results from the German Competence Network CAPNETZ. *Thorax* 2010; 65: 208–214.
114. Rello J, Lisboa T, Lujan M, *et al.* Severity of pneumococcal pneumonia associated with genomic bacterial load. *Chest* 2009; 136: 832–840.
115. Peters RP, de Boer RF, Schuurman T, *et al. Streptococcus pneumoniae* DNA load in blood as a marker of infection in patients with community-acquired pneumonia. *J Clin Microbiol* 2009; 47: 3308–3312.
116. Lisboa T, Waterer G, Rello J. We should be measuring genomic bacterial load and virulence factors. *Crit Care Med* 2010; 38: Suppl. 10, S656–S662.

Chapter 8

CAP phenotypes

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SUMMARY: During recent decades, specific phenotypes of patients with community-acquired pneumonia (CAP) have been described, exerting distinctive clinical features, severity, aetiology and outcome. Today, CAP in the elderly (⩾65 years) clearly forms the core group within the concept of CAP. Clinical presentation may be oligosymptomatic, and comorbid conditions are present in a high proportion of patients. In contrast, CAP in younger patients (<65 years) has a more typical clinical presentation. Mortality is low and *Mycoplasma pneumoniae* is the second most common pathogen. The main feature of nursing home-acquired pneumonia is a very high mortality, which is mainly driven by poor functional status. Clinical presentation of patients with CAP and chronic obstructive pulmonary disease (COPD) is typically more severe, despite a similar mortality compared to patients without COPD. In addition, *Pseudomonas aeruginosa* has to be taken into account in patients with severe COPD. Aspiration as a cause of pneumonia is underdiagnosed. Patients suffering from dysphagia, for example, are at risk of recurrent pneumonia.

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Today, community-acquired pneumonia (CAP) is primarily a disease of the elderly [1]. During recent decades, several subgroups have been identified with their own phenotypes due to age, comorbidity and functional status: CAP in the elderly [2], nursing home-acquired pneumonia (NHAP) [3], CAP in the very elderly [4] and CAP in younger patients [5]. In ageing societies with increasing life expectancy, elderly and disabled patients clearly form the core group within the concept of CAP, rendering younger patients as a relevant subgroup [6]. Moreover, CAP in chronic obstructive pulmonary disease (COPD) patients exerts some typical patterns different to those seen in patients without COPD, and community-acquired aspiration pneumonia exerts some peculiarities.

Patients with lung cancer or other solid cancers affecting the lung are usually included in series evaluating patients with CAP. Surprisingly, we are not aware of a single study addressing this group specifically. CAP in HIV-infected patients has recently been extensively reviewed [7]. It appears that in patients with CD4 counts above 200 cells·μL^{-1} there are no differences in presentation of pneumonia compared with the non-HIV-infected population, whereas in those with lower CD4 cell counts differences are striking, justifying inclusion of these patients in the group of "pneumonia in the immunosuppressed host". Also, different gene polymorphisms have been shown to be associated with CAP severity, which may be regarded as a genetic "phenotype" [8]. This approach seems promising; however, much more work needs to be dedicated to genetic polymorphisms in order to conduct a clinically meaningful genetic CAP phenotype.

This chapter highlights characteristics of different CAP phenotypes according to clinical presentation, severity, microbiological aetiology and outcome.

CAP in the elderly

CAP in the elderly (usually $\geqslant$65 years) clearly forms the core group within the concept of CAP. Elderly patients are more susceptible to CAP and the incidence increases with each decade of age, from <100 in those patients younger than 50 years reaching >3500 patients per 100 000 inhabitants per year in those aged 90 years or older for hospitalised CAP [1]. In a German database originating from a nationwide quality assurance programme, comprising all hospitalised cases with CAP over a 3-year period (n=660 594), 77% of patients were aged 65 years or older [9].

In elderly patients with CAP, clinical presentation may be oligosymptomatic. Typical symptoms may be absent in a relevant proportion of patients [2, 10–12]. For example, the prevalence of fever in elderly patients with CAP at initial presentation has been reported to be as low as approximately 30% by some authors [2, 12]. The presence of typical symptoms such as fever and pleuritic chest pain at initial presentation decreases with age [4, 5, 10]. Instead, the proportion of patients presenting with confusion is higher in the elderly [4, 5]. In some cases, a new onset altered mental status or signs of decompensation of pre-existing illnesses may be the only obvious symptoms [11]. As a consequence, diagnosis of CAP may be delayed in a relevant proportion of elderly patients [11, 13]. However, the physician needs a high level of suspicion for CAP in elderly patients presenting to the emergency department [14].

Mortality of CAP clearly increases with age [1, 5, 15]. In hospitalised elderly patients with CAP, 30-day or in-hospital mortality reaches 8–17% [4, 5, 12, 15–22], and long-term mortality reaches 19% at 6 months [5] and 41% at 1 year [17]. Depending on severity and proportion of nursing home residents included, a short-term mortality of 26% ranging to more than 50% has been described [2, 23–25].

A study from Finland comprising 4167 elderly patients with CAP and a median follow-up of 9.2 years indicated an increased risk death for several years following an episode of CAP in the elderly [26]. In fact, CAP is a common cause of death in the elderly. Most elderly patients presenting with CAP suffer from comorbid conditions. The rate of those patients with at least one comorbidity is usually 80% or higher [5, 12, 15, 18, 27]. The most common comorbidities are chronic pulmonary and cardiac diseases, diabetes and neurological illnesses [4, 10, 12, 15–18, 24, 27–29]. Additionally, malnutrition [11, 12, 23] and impairment of functional status [18, 24, 30, 31] are common problems in this population and are associated with a poor prognosis. Several independent risk factors for death in elderly patients with CAP have been previously described (table 1) [4, 12, 15, 18, 20, 21, 23–25, 29, 30].

As regards aetiology, the proportion of patients with a microbiological diagnosis decreases with age [5, 15]. However, aetiology in elderly patients with CAP is usually comparable to a general population, with *Streptococcus pneumoniae* being the most frequent pathogen. Only a low rate of potential multidrug-resistant (MDR) pathogens, such as Gram-negative bacteria and *Staphylococcus aureus*, has been reported in the elderly [2, 15, 18, 24, 29]. Some studies with a higher proportion of potential MDR strains obviously suffer from methodological problems in assessing notoriously impure samples such as sputum [10, 12, 25]. Nevertheless, since the presence of potential MDR pathogens is independently associated with death [4, 15], a careful assessment for individual risk factors is advocated. In a Spanish study including 2149 elderly patients with CAP, excluding nursing home residents, CILLÓNIZ *et al.* [15] found *Haemophilus influenzae* to be more frequent in patients with at least one comorbidity, while *Legionella pneumophila* was more frequent in those without comorbidity. Potential MDR pathogens were found almost exclusively in patients with one or more comorbid condition. Moreover, an association of increasing mortality with an increasing number of comorbidities was noted. The authors concluded that comorbidities, not age, are associated with specific aetiologies, and that mortality in the elderly is mainly associated with the presence of comorbidities and potential MDR pathogens [15].

CAP in younger patients

Whereas a lot of studies specifically addressed CAP in the elderly during the past decades, less attention has been paid to younger patients (<65 years). In contrast to CAP in the elderly, clinical presentation in younger patients presenting with CAP is more typical. Recently, a large German database comprising 7803 ambulatory and hospitalised patients showed that younger patients with CAP markedly differ from the elderly in terms of clinical presentation, comorbidity, severity, aetiology and outcome [5].

Typical symptoms such as fever and pleuritic chest pain were more common in younger patients, whereas confusion, dyspnoea, tachypnoea and pleural effusion were less prevalent. Frequency of comorbidities in younger patients was 50% less compared to the elderly (47% *versus* 88%).

S. pneumoniae was the most frequent pathogen, followed by *Mycoplasma pneumoniae*. The latter was the most frequently detected species in younger patients treated on an outpatient basis and in younger patients without comorbidity. Overall, severity was mild to moderate in most cases. Short-term (within 30 days), as well as long-term (within 180 days) mortality was four-fold lower in younger patients (1.7% *versus* 8.2% and 3.0% *versus* 9.9%, respectively). Most differences arose within the fifth or the middle of the sixth decade.

Table 1. Independent risk factors for death in elderly patients with community-acquired pneumonia

Independent risk factors	[Ref.]
Host factors	
Advanced age	[15, 21, 29]
Nursing home resident	[21, 29]
Prior low functional status	[18, 24, 30]
Prior swallowing disorders	[24]
Neurological disease	[15, 29]
Renal insufficiency	[4]
Chronic liver disease	[29]
Clinical findings/severity	
New onset confusion	[4, 12, 18]
Absence of chills	[18]
Absence of fever	[12, 20, 24]
Tachypnoea	[12, 24]
Tachycardia	[20]
Bacteraemia	[15]
Bilateral infiltrates	[12, 20]
Multilobar involvement	[21, 24, 25]
Rapid radiological spread	[23]
PSI class IV–V	[15]
CURB	[29]
APACHE II score >22	[23]
ICU admission	[15]
Impaired oxygenation on admission	[18]
Elevated blood urea nitrogen	[12]
Creatinine >1.4 mg·dL^{-1}	[18]
Aetiology	
Potential MDR pathogen	[15]
Gram-negative bacteria	[4]
Complications	
Pleural effusion	[20]
(Septic) shock	[4, 12, 25]
Respiratory failure	[4]
Mechanical ventilation	[21]
Renal failure	[18, 23, 25]
Number of complications	[21]
Ineffective/inadequate antimicrobial treatment	[25, 29]
Others	
Number of antimicrobial substances used	[21]

PSI: Pneumonia Severity Index; CURB: confusion, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) or ⩽60 mmHg (diastolic); APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit; MDR: multidrug resistant.

Taken together, it appears that younger and elderly patients form different phenotypes of CAP. However, the main differences do not relate to aetiology (which seems to be mainly driven by comorbidity) but to clinical presentation and outcome [5].

Nursing home-acquired pneumonia

With increasing life-expectancy, there is an increased number of disabled and dependent people, of whom a relevant proportion live in long-term care facilities. These patients are particularly prone to

develop pneumonia. The term NHAP was first introduced in 1978 by GARB *et al.* [3]. Since then, NHAP has become an accepted phenotype of CAP. However, things are not as clear in Europe.

Without doubt, NHAP is the leading cause of morbidity in nursing home residents and is a frequent terminal event [32]. The incidence of NHAP is reported to reach 9900–91 200 per 100 000 persons per year, considerably higher than in the remaining population [33].

There are several specific features in patients with NHAP. Most patients presenting with NHAP suffer from multiple comorbid conditions. At least one comorbidity is present in 89–97% of patients with NHAP [19, 34–36], with predominantly neurological and cardiac illnesses being reported [20, 22, 35–38]. In studies comparing NHAP with CAP, the frequency of comorbid conditions is clearly higher in nursing home residents [20, 35, 36]. Consequently, the functional status of nursing home residents with CAP in terms of mobility and self-sufficiency is lower compared with patients with CAP residing in their own homes [19, 20, 22, 39].

Compared with CAP in general, patients with NHAP present with fewer symptoms that are typical of pneumonia, *e.g.* cough, purulent sputum and chest pain are less frequent [19, 21, 25, 36]. Instead, in the proportion of patients with new-onset confusion is significantly higher [19–21, 25, 35, 36, 39]. In contrast to these findings, pneumonia in nursing home residents is usually more severe according to clinical presentation and risk scores [20, 22, 35, 36, 39].

In a study performed by MUDER *et al.* [40] with 108 patients suffering from NHAP, an inverse correlation of increasing mortality with decreasing functional status was observed. Short-term mortality was 5% for those with an Activities of Daily Living (ADL) index <11 and increased to 27% in those with an ADL index >15 according to KATZ *et al.* [41]. In fact, functional status is the main determinant for outcome in nursing home residents who develop pneumonia [40].

A typical finding in studies investigating NHAP is quite a high mortality and a comparatively low rate of ventilator support [19, 36, 40, 42]. These inverse relationships hint at hidden treatment restrictions in patients with NHAP, which is often a terminal event in nursing home residents [42]. As a consequence of a low functional status and hidden or documented treatment restriction, mortality is dramatically high in NHAP compared with CAP other than NHAP. Short-term (30-day or in-hospital) mortality is reported to be 12–53% depending on the degree of severity and functional impairment [1, 9, 19, 21, 22, 34–36, 38, 43–48], and long-term mortality is reported to be 44% at 6 months [36] and nearly 60% at 1 year [19, 39]. In a German study, short- (30-day) and long-term (180-day) mortality was nearly four- and three-fold higher, respectively, in NHAP compared with CAP other than NHAP [36]. Several risk factors for death in patients with NHAP have been identified (table 2) [19, 38, 40].

There is an ongoing controversy as to whether the aetiology of patients with NHAP differs from those with other forms of CAP.

S. pneumoniae is the leading pathogen and cases of potential MDR pathogens such as Gram-negative bacteria and *S. aureus* are rare [20, 35, 36, 38]. Recently, no major differences in microbiological findings were seen when comparing patients aged 65 years or older with NHAP to those with CAP other than NHAP. Moreover, potential MDR pathogens were rare (Gram-negative bacteria and *S. aureus* were both $<5\%$ and overall there were only two cases with methicillin-resistant *S. aureus*) [36]. At least three additional recent studies could not a find an excess of potential MDR pathogens in patients with NHAP [35, 38, 49].

However, caution is needed when interpreting pathogen patterns in NHAP patients. First, the definition of "nursing home" is not standardised, and may include a wide range of different settings of care. Secondly, the comorbidity status varies across studies and, in particular, in the number of patients with severe immunosuppression. Finally, methodology of microbiological investigation has a heavy impact on the rate of Gram-negative bacteria and *Pseudomonas aeruginosa*. In a study by VON BAUM *et al.* [50], it was shown that the rate of these pathogens decreases strikingly when only high-quality sputum samples were accepted. Importantly, there was an excess rate of mortality only in the group with these pathogens detected in high-quality samples, supporting the relevance of quality criteria [50].

The frequency of aspiration as a cause of pneumonia in nursing home residents is higher compared with patients living at home [21, 35]. This can mainly be explained by a higher rate of neurological comorbidity.

Table 2. Independent risk factors for death in nursing home-acquired pneumonia

Independent risk factors	[Ref.]
Host factors	
Self-insufficiency at time of admission	[19]
ADL score >15	[40, 41]
Neurological diseases	[38]
Aetiology	
Gram-negative bacteria/MRSA	[38]
Complications	
Septic shock	[38]
Pleural effusion	[38]
Complications during hospital stay	[19]

ADL: activities of daily living; MRSA: methicillin-resistant *Staphylococcus aureus*.

Since comorbidity and functional impairment increase with age, the typical patient with NHAP has clearly reached an advanced age. Nevertheless, we found a relevant proportion of younger patients in a German cohort with 618 cases of NHAP [42]. Overall, 16% of all patients with NHAP were younger than 65 years of age. These patients differed fundamentally in terms of comorbidity, symptoms at initial presentation and outcome to those aged 65 years or older. Whereas virtually all elderly patients suffered from at least one comorbid condition, the rate in younger patients and the mean number of conditions was significantly lower compared with the elderly. Moreover, the pattern of comorbidity was different. In both younger and elderly patients, neurological disorders were the most common illnesses. Whereas cerebrovascular disease and cardiac illnesses were the most frequent disorders in the elderly, younger patients mostly suffered from other neurological diseases and cardiac comorbidities were rare. Fever was significantly more prevalent in younger patients. Both, short- and long-term mortality were twice as high in the elderly. Thus, age is also a factor affecting clinical presentation and outcome in patients with NHAP [42].

Healthcare-associated pneumonia

In 2005, the Infectious Disease Society of America/American Thoracic Society guidelines for the management of adults with nosocomial pneumonia have included a new entity called healthcare-associated pneumonia (HCAP) [51]. The main hypothesis of the HCAP concept is that patients meeting such criteria (essentially NHAP patients and patients who have comorbid conditions with repeated contact with healthcare services, particularly frequent hospitalisation and antimicrobial treatment) have an excess mortality compared with CAP due to specific pathogen patterns (including MDR pathogens) otherwise not covered by empirical initial antimicrobial treatment in current guidelines [6, 52]. In fact, the first study on HCAP reported extremely high rates of potential MDR strains in such patients and mortality rates reaching those of nosocomial pneumonia [53].

This concept has been subject to criticism. First, such high excess rates of potential MDR pathogens could not be found in any subsequent study, neither in the USA, Japan, Korea nor Europe [52]. In a recent meta-analysis, it could be shown that even excess mortality rates disappeared when adjusted for comorbidity [54]. No study has proven a link between the presence of potential MDR pathogens and mortality; however, functional status seems to be the main driver of mortality [52].

Overall, it appears that the HCAP concept should not be adopted as a fourth category of pneumonia [6, 55].

Special considerations

Two more groups of patients deserve attention: CAP in patients with COPD and those with aspiration pneumonia both have unique features that are worthy of recognition.

CAP in patients with COPD

COPD is a major cause of morbidity and mortality in western societies [56]. The pathophysiology of this disease comprises a chronic airway inflammation causing mucus hypersecretion and airflow limitation. Triggered by infection or other environmental factors, acute exacerbations of COPD (AECOPD) frequently occur in patients suffering from COPD. AECOPD is characterised clinically by increased symptoms such as dyspnoea, cough and sputum production [56]. Obviously, all these symptoms can also be caused by pneumonia. Thus, in order to differentiate both entities the presence or absence of a new or increased infiltrate on chest radiograph is mandatory. Clearly, there is an overlap between both entities and an unambiguous diagnosis cannot be obtained in all cases.

Among patients with COPD the risk for pneumonia is significantly increased [57–59]. SORIANO *et al.* [57] found a relative risk of 16 for developing pneumonia in patients with COPD compared to those without COPD. COPD is a common comorbidity in hospitalised patients with CAP with a frequency of 15–36% of cases [60–63].

Patients with COPD hospitalised for CAP are older and predominantly male compared with those patients without COPD [61–65]. Other comorbid conditions such as chronic heart disease are more prevalent [62–65]. As regards clinical presentation, a higher rate of sputum production [61, 63] and a lower rate of fever [60, 61, 63] at initial presentation have been described in patients with COPD and CAP. Generally, severity in patients with CAP and COPD is higher compared to those without COPD. A higher Pneumonia Severity Index (PSI) score [60–62, 64], and a higher rate of tachypnoea [60, 63] and respiratory failure [61, 64] have also been described. However, no differences in terms of CURB65 (confusion, urea >7 mmol·L^{-1}, respiratory rate $\geqslant 30$ breaths·min^{-1}, blood pressure <90 mmHg (systolic) or $\leqslant 60$ mmHg (diastolic), age $\geqslant 65$ years) scores were found [60, 62]. Recently, LIAPIKOU *et al.* [60] published the largest study to date, addressing the differences of patients hospitalised with CAP with and without COPD. Prospective data of 1379 patients with CAP including 212 patients with COPD confirmed by spirometry prior to admission were analysed. Patients with COPD were predominantly male, were more likely to have previously received antimicrobial therapy, and CAP was more severe according to PSI and tachypnoea. However, patients with COPD had less multilobar infiltration and experienced fewer pulmonary complications. Despite a higher severity of CAP in patients with COPD, mortality was equal with a trend to a better outcome in patients with COPD (4.2% *versus* 7%, $p=0.14$) [60]. This seemingly conflicting finding might be explained by the fact that patients with COPD might achieve higher severity scores even in the presence of a relatively limited inflammatory response and extension of pneumonia on a pre-existing pulmonary compromise.

Overall, short-term mortality in patients with CAP and COPD was found to reach 4–13% [60–64, 66] and was up to 30% for patients admitted to an intensive care unit (ICU) [65]. Studies comparing mortality of hospitalised patients suffering from CAP with and without COPD revealed conflicting results. Some authors found equal mortality rates [60, 62, 63], whereas others found a higher mortality in those patients with COPD [61, 64, 65]. However, two studies that found a higher mortality for patients with CAP and COPD had a retrospective design and diagnosis was not confirmed by spirometry [64, 65]. This is highly relevant as, in a study by SNIJDERS *et al.* [62] evaluating patients with CAP with and without COPD confirmed by spirometry, diagnosis of COPD was rejected after spirometry in 30.5% of patients with a reported diagnosis of COPD while in 17.4% of all patients without a past medical history of COPD a new diagnosis was established after spirometry.

As in general populations with CAP, *S. pneumoniae* is the most prevalent pathogen in patients with COPD and CAP [60–65]. Possible differences regarding aetiology of CAP refer to a higher rate of Gram-negative bacteria [63] including *P. aeruginosa* [60, 63–65, 67] in patients with severe COPD.

Aspiration pneumonia

Aspiration pneumonia is a complex topic and is difficult to diagnose. Following aspiration, both aspiration pneumonitis (a chemical pneumonitis) and aspiration pneumonia (an infectious process) can occur [68]. Both are distinct entities. In this section, we focus on the latter.

According to the 2011 European Respiratory Society guidelines for the management of adult lower respiratory tract infection [69], diagnosis of aspiration pneumonia should be suspected in patients with CAP: 1) following a witnessed episode of aspiration; or 2) in the presence of risk factors for aspiration, including reduced level of consciousness and dysphagia due to mechanical or neurological upper digestive tract dysfunction. In fact, similar definitions are used by most studies addressing this topic [4, 21, 24, 67, 70–73].

Aspiration pneumonia is estimated to be a cause of CAP in up to 23% of cases [4, 21, 24, 67, 70, 71, 73]. However, aspiration pneumonia seems underdiagnosed, particularly in the elderly [74]. In a study performed by KIKUCHI *et al.* [75], 14 elderly patients with CAP and 10 age-matched controls were assessed for silent aspiration during sleep using a radioactive tracer. Silent aspiration occurred in 71% of elderly patients with CAP *versus* only 10% in the control group. This finding indicates a major role of silent aspiration for the development of CAP in the elderly. In another study investigating the prevalence of aspiration pneumonia in hospitalised patients with pneumonia (both CAP and hospital-acquired pneumonia) assessing swallowing function, TERAMOTO *et al.* [76] found an overall prevalence of aspiration pneumonia in patients with CAP of 60% and an even higher percentage for patients with hospital-acquired pneumonia, which increased with age. Investigating the cough reflex of five patients with aspiration pneumonia compared with 10 age-matched controls using increasing concentrations of citric acid, SEKIZAWA *et al.* [77] found decreased cough reflex in patients with aspiration pneumonia. While all controls coughed at some point, none of the patients with aspiration pneumonia coughed, even at the highest concentration, hinting at reduced cough reflex as an important pathophysiological factor for aspiration pneumonia [77]. Also, a prior swallowing disorder was found as a risk factor for CAP in the elderly [24] and aspiration pneumonia has been described as a risk factor for 18-month readmission due to pneumonia [30]. In a recent study, ALMIRALL *et al.* [78] studied the role of dysphagia in 36 elderly patients with CAP and 71 age- and sex-matched controls. They found a significantly higher rate of oropharyngeal dysphagia in cases compared with controls (92% *versus* 40%). Furthermore, in the CAP patients, impaired swallowing was a prognostic factor for a worse outcome at 1 year [78]. Taken together, there is strong evidence that aspiration pneumonia is underdiagnosed and that patients with a pre-existing swallowing disorder or an altered cough reflex are at risk for recurrent episodes of pneumonia.

In a study including 505 patients with CAP admitted to an ICU, including 116 patients with suspected aspiration due to usual criteria, LEROY *et al.* [71] found altered mental status (due to drug overdose, intoxication, seizures, *etc.*) to be the most frequent cause (77%) of aspiration pneumonia, followed by impaired airways reflexes and/or gastrointestinal problems in 19%, and witnessed large aspiration in only 5%.

Several studies from the 1970s addressing aspiration pneumonia using trans-tracheal aspiration found a huge proportion of anaerobic strains [70, 79–81]. This is most likely due to a delay in microbiological investigations, a high rate of patients with chronic alcoholism in these studies and a possible contamination of trans-tracheal aspirates by oropharyngeal flora [82]. Scarce recent data regarding the aetiology of community-acquired aspiration pneumonia indicate that anaerobic strains are very rare and that microbiological findings resemble the spectrum found in CAP [83, 84].

In a study investigating the microbiology of severe aspiration pneumonia in 95 nursing home residents admitted to the ICU, EL-SOLH *et al.* [72] found an impaired functional status to be the only determinant for anaerobic pathogens. All patients suffered from comorbid conditions, with cerebrovascular disease as the most frequent illness (78%). An impaired functional status as well as

a low serum albumin as a surrogate for an impaired nutritional status were independently associated with poor outcome [72].

Conclusion

In summary, CAP in the elderly (aged 65 years or greater) forms the core group within the concept of CAP. In elderly patients with CAP, symptoms may be subtle and, in some cases, decompensation of pre-existing illnesses may cause the only obvious symptoms. CAP in younger patients (aged less than 65 years) forms a relevant subgroup. In contrast to the elderly, younger patients with CAP present with more typical symptoms. *M. pneumoniae* is found in a huge proportion of patients. Comorbidity plays a minor role and mortality is comparatively low. The main characteristic in NHAP is the considerably higher mortality, which is mainly driven by an impaired functional status. Virtually all patients suffer from comorbid conditions. NHAP is frequently a terminal event and documented or hidden treatment restrictions are present in a relevant proportion of patients. Looking at patients with COPD, there is an overlap between CAP and AECOPD. Both entities can only be differentiated by chest radiograph. Patients with CAP and COPD present more often with sputum production and less frequently with fever. Despite a higher severity, mortality is comparable to those patients without COPD. The frequency of Gram-negative bacteria and in particular *P. aeruginosa* is higher in patients with CAP and severe COPD. Aspiration pneumonia is clearly underdiagnosed. Those patients with a swallowing disorder or an impaired cough reflex are at risk of recurrent pneumonia. Anaerobic pathogens are very rare and the only independent risk factor for these strains is an impaired functional status.

Approach to management

In patients presenting to the emergency department, CAP should be suspected in the presence of typical symptoms like cough, sputum production, fever, dyspnoea or pleuritic chest pain, and should be confirmed or ruled out by chest radiograph. In patients with altered mental status or decompensated underlying disease, the presence of CAP should be considered even in the absence

Table 3. Risk factors for potential multidrug-resistant pathogens

First author [ref.]	Setting	Strain	Risk factor
Ruiz [67]	Hospitalised CAP	GNB including *P. aeruginosa* *P. aeruginosa*	Pulmonary comorbidity Severe pneumonia (ICU admission) Pulmonary comorbidity
Arancibia [89]	Hospitalised CAP	GNB including *P. aeruginosa* *P. aeruginosa*	Probable aspiration Previous hospital admission Previous antimicrobial treatment (within 30 days before presentation) Pulmonary comorbidity Pulmonary comorbidity Previous hospital admission
Falguera [90]	Hospitalised CAP	GNB including *P. aeruginosa*	Septic shock Use of corticosteroids Prior antimicrobial treatment (within 48 h before presentation) COPD Tachypnoea
von Baum [50]	Hospitalised and ambulatory CAP	GNB other than *P. aeruginosa* *P. aeruginosa*	Congestive heart failure Cerebrovascular disease Chronic respiratory disease Enteral tube feeding

CAP: community-acquired pneumonia; GNB: Gram-negative bacteria; *P. aeruginosa*: *Pseudomonas aeruginosa*; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease.

of typical signs and symptoms for pneumonia. This is particularly true for elderly patients [11]. After diagnosis of CAP has been confirmed, an assessment of severity should follow immediately. Different scores for this purpose have been developed, such as the PSI [85], and CURB (confusion, urea >7 mmol·L^{-1}, respiratory rate $\geqslant 30$ breaths·min^{-1}, blood pressure <90 mmHg (systolic) or $\leqslant 60$ mmHg (diastolic)) and its variations [86, 87]. Both have shown to predict mortality accurately [88]. We advocate using the CRB65 score (confusion, respiratory rate $\geqslant 30$ breaths·min^{-1}, blood pressure <90 mmHg (systolic) or $\leqslant 60$ mmHg (diastolic), age $\geqslant 65$ years) because of its simplicity, consisting of only four parameters, which are immediately available in the emergency department without needing laboratory measurements [88]. One point is given for each parameter at initial presentation, resulting in scores ranging from 0 to 4. According to the risk predicted by the score in combination with the clinical presentation, site of care should be defined (ambulatory, regular ward or ICU). Every patient should be assessed regarding the risk of potential MDR pathogens. Several risk factors for potential MDR pathogens have been identified (table 3) [50, 67, 89, 90]. Antimicrobial treatment should be chosen according to severity and individual risk factors. The first dose should be administered within 8 h of hospital admission in otherwise stable patients [91], and within 1 h in patients with severe sepsis or septic shock [92].

Statement of Interest

A. Torres has received consultancy fees from Astellas.

References

1. Ewig S, Birkner N, Strauss R, *et al.* New perspectives on community-acquired pneumonia in 388406 patients. Results from a nationwide mandatory performance measurement programme in healthcare quality. *Thorax* 2009; 64: 1062–1069.
2. Venkatesan P, Gladman J, Macfarlane JT, *et al.* A hospital study of community acquired pneumonia in the elderly. *Thorax* 1990; 45: 254–258.
3. Garb JL, Brown RB, Garb JR, *et al.* Differences in etiology of pneumonias in nursing home and community patients. *JAMA* 1978; 240: 2169–2172.
4. Fernández-Sabé N, Carratalà J, Rosón B, *et al.* Community-acquired pneumonia in very elderly patients: causative organisms, clinical characteristics, and outcomes. *Medicine (Baltimore)* 2003; 82: 159–169.
5. Klapdor B, Ewig S, Pletz MW, *et al.* Community-acquired pneumonia in younger patients is an entity on its own. *Eur Respir J* 2012; 39: 1156–1161.
6. Ewig S, Welte T, Chastre J, *et al.* Rethinking the concepts of community-acquired and health-care-associated pneumonia. *Lancet Infect Dis* 2010; 10: 279–287.
7. Benito N, Moreno A, Miro JM, *et al.* Pulmonary infections in HIV-infected patients: an update in the 21st century. *Eur Respir J* 2012; 39: 730–745.
8. Waterer GW, Quasney MW, Cantor RM, *et al.* Septic shock and respiratory failure in community-acquired pneumonia have different TNF polymorphism associations. *Am J Respir Crit Care Med* 2001; 163: 1599–1604.
9. Ewig S, Bauer T, Richter K, *et al.* Prediction of in-hospital death from community-acquired pneumonia by varying CRB-age groups. *Eur Respir J* 2013; 41: 917–922.
10. Metlay JP, Schulz R, Li YH, *et al.* Influence of age on symptoms at presentation in patients with community-acquired pneumonia. *Arch Intern Med* 1997; 157: 1453–1459.
11. Riquelme R, Torres A, el-Ebiary M, *et al.* Community-acquired pneumonia in the elderly. Clinical and nutritional aspects. *Am J Respir Crit Care Med* 1997; 156: 1908–1914.
12. García-Ordóñez MA, García-Jiménez JM, Páez F, *et al.* Clinical aspects and prognostic factors in elderly patients hospitalised for community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis* 2001; 20: 14–19.
13. Waterer GW, Kessler LA, Wunderink RG. Delayed administration of antibiotics and atypical presentation in community-acquired pneumonia. *Chest* 2006; 130: 11–15.
14. Brito V, Niederman MS. How can we improve the management and outcome of pneumonia in the elderly? *Eur Respir J* 2008; 32: 12–14.
15. Cillóniz C, Polverino E, Ewig S, *et al.* Impact of age and comorbidity on cause and outcome in community-acquired pneumonia. *Chest* 2013; 144: 999–1007.
16. Kaplan V, Angus DC, Griffin MF, *et al.* Hospitalized community-acquired pneumonia in the elderly: age- and sex-related patterns of care and outcome in the United States. *Am J Respir Crit Care Med* 2002; 165: 766–772.
17. Kaplan V, Clermont G, Griffin MF, *et al.* Pneumonia: still the old man's friend? *Arch Intern Med* 2003; 163: 317–323.
18. Zalacain R, Torres A, Celis R, *et al.* Community-acquired pneumonia in the elderly: Spanish multicentre study. *Eur Respir J* 2003; 21: 294–302.

19. Marrie TJ, Blanchard W. A comparison of nursing home-acquired pneumonia patients with patients with community-acquired pneumonia and nursing home patients without pneumonia. *J Am Geriatr Soc* 1997; 45: 50–55.
20. Lim WS, Macfarlane JT. A prospective comparison of nursing home acquired pneumonia with community acquired pneumonia. *Eur Respir J* 2001; 18: 362–368.
21. Marrie TJ, Durant H, Yates L. Community-acquired pneumonia requiring hospitalization: 5-year prospective study. *Rev Infect Dis* 1989; 11: 586–599.
22. Meehan TP, Chua-Reyes JM, Tate J, *et al.* Process of care performance, patient characteristics, and outcomes in elderly patients hospitalized with community-acquired or nursing home-acquired pneumonia. *Chest* 2000; 117: 1378–1385.
23. Rello J, Rodriguez R, Jubert P, *et al.* Severe community-acquired pneumonia in the elderly: epidemiology and prognosis. Study Group for Severe Community-Acquired Pneumonia. *Clin Infect Dis* 1996; 23: 723–728.
24. Riquelme R, Torres A, El-Ebiary M, *et al.* Community-acquired pneumonia in the elderly: a multivariate analysis of risk and prognostic factors. *Am J Respir Crit Care Med* 1996; 154: 1450–1455.
25. El-Solh AA, Sikka P, Ramadan F, *et al.* Etiology of severe pneumonia in the very elderly. *Am J Respir Crit Care Med* 2001; 163: 645–651.
26. Koivula I, Stén M, Mäkelä PH. Prognosis after community-acquired pneumonia in the elderly: a population-based 12-year follow-up study. *Arch Intern Med* 1999; 159: 1550–1555.
27. Fry AM, Shay DK, Holman RC, *et al.* Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988–2002. *JAMA* 2005; 294: 2712–2719.
28. Marrie TJ. Epidemiology of community-acquired pneumonia in the elderly. *Semin Respir Infect* 1990; 5: 260–268.
29. Kothe H, Bauer T, Marre R, *et al.* Outcome of community-acquired pneumonia: influence of age, residence status and antimicrobial treatment. *Eur Respir J* 2008; 32: 139–146.
30. Torres OH, Muñoz J, Ruiz D, *et al.* Outcome predictors of pneumonia in elderly patients: importance of functional assessment. *J Am Geriatr Soc* 2004; 52: 1603–1609.
31. Loeb M, Neupane B, Walter SD, *et al.* Environmental risk factors for community-acquired pneumonia hospitalization in older adults. *J Am Geriatr Soc* 2009; 57: 1036–1040.
32. El-Solh AA. Nursing home acquired pneumonia: approach to management. *Curr Opin Infect Dis* 2011; 24: 148–151.
33. Muder RR. Pneumonia in residents of long-term care facilities: epidemiology, etiology, management, and prevention. *Am J Med* 1998; 105: 319–330.
34. Naughton BJ, Mylotte JM, Ramadan F, *et al.* Antibiotic use, hospital admissions, and mortality before and after implementing guidelines for nursing home-acquired pneumonia. *J Am Geriatr Soc* 2001; 49: 1020–1024.
35. Garcia-Vidal C, Viasus D, Roset A, *et al.* Low incidence of multidrug-resistant organisms in patients with healthcare-associated pneumonia requiring hospitalization. *Clin Microbiol Infect* 2011; 17: 1659–1665.
36. Ewig S, Klapdor B, Pletz MW, *et al.* Nursing-home-acquired pneumonia in Germany: an 8-year prospective multicentre study. *Thorax* 2012; 67: 132–138.
37. Kruse RL, Mehr DR, Boles KE, *et al.* Does hospitalization impact survival after lower respiratory infection in nursing home residents? *Med Care* 2004; 42: 860–870.
38. Polverino E, Dambrava P, Cillóniz C, *et al.* Nursing home-acquired pneumonia: a 10 year single-centre experience. *Thorax* 2010; 65: 354–359.
39. Muder RR, Aghababian RV, Loeb MB, *et al.* Nursing home-acquired pneumonia: an emergency department treatment algorithm. *Curr Med Res Opin* 2004; 20: 1309–1320.
40. Muder RR, Brennen C, Swenson DL, *et al.* Pneumonia in a long-term care facility. A prospective study of outcome. *Arch Intern Med* 1996; 156: 2365–2370.
41. Katz S, Downs TD, Cash HR, *et al.* Progress in development of the index of ADL. *Gerontologist* 1970; 10: 20–30.
42. Klapdor B, Ewig S, Schaberg T, *et al.* Presentation, etiology and outcome of pneumonia in younger nursing home residents. *J Infect* 2012; 65: 32–38.
43. Man SY, Graham CA, Chan SSW, *et al.* Disease severity prediction for nursing home-acquired pneumonia in the emergency department. *Emerg Med J* 2011; 28: 1046–1050.
44. El Solh AA, Akinnusi ME, Alfarah Z, *et al.* Effect of antibiotic guidelines on outcomes of hospitalized patients with nursing home-acquired pneumonia. *J Am Geriatr Soc* 2009; 57: 1030–1035.
45. Maruyama T, Niederman MS, Kobayashi T, *et al.* A prospective comparison of nursing home-acquired pneumonia with hospital-acquired pneumonia in non-intubated elderly. *Respir Med* 2008; 102: 1287–1295.
46. Maruyama T, Gabazza EC, Morser J, *et al.* Community-acquired pneumonia and nursing home-acquired pneumonia in the very elderly patients. *Respir Med* 2010; 104: 584–592.
47. El-Solh AA, Aquilina AT, Dhillon RS, *et al.* Impact of invasive strategy on management of antimicrobial treatment failure in institutionalized older people with severe pneumonia. *Am J Respir Crit Care Med* 2002; 166: 1038–1043.
48. Marrie TJ, Durant H, Kwan C. Nursing home-acquired pneumonia. A case-control study. *J Am Geriatr Soc* 1986; 34: 697–702.
49. Ma HM, Wah JLS, Woo J. Should nursing home-acquired pneumonia be treated as nosocomial pneumonia? *J Am Med Dir Assoc* 2012; 13: 727–731.
50. Von Baum H, Welte T, Marre R, *et al.* Community-acquired pneumonia through *Enterobacteriaceae* and *Pseudomonas aeruginosa*: diagnosis, incidence and predictors. *Eur Respir J* 2010; 35: 598–605.

51. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171: 388–416.
52. Ewig S, Welte T, Torres A. Is healthcare-associated pneumonia a distinct entity needing specific therapy? *Curr Opin Infect Dis* 2012; 25: 166–175.
53. Kollef MH, Shorr A, Tabak YP, *et al.* Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest* 2005; 128: 3854–3862.
54. Chalmers JD, Rother C, Salih W, *et al.* Healthcare associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. *Clin Infect Dis* 2013 [In press DOI: 10.1093/cid/cit734].
55. Ewig S. The pneumonia triad. *In:* Chalmers JD, Pletz MW, Aliberti S, eds. Community-Acquired Pneumonia. *Eur Respir Monogr* 2014; 63: 13–24.
56. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. www.goldcopd.org/uploads/users/files/GOLD-_Report-_2013_Feb20.pdf Date last updated: February 20, 2013.
57. Soriano JB, Visick GT, Muellerova H, *et al.* Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005; 128: 2099–2107.
58. Torres A, Ewig S. The strange case of community-acquired pneumonia in COPD. *Chest* 2011; 139: 483–485.
59. Almirall J, Bolíbar I, Serra-Prat M, *et al.* New evidence of risk factors for community-acquired pneumonia: a population-based study. *Eur Respir J* 2008; 31: 1274–1284.
60. Liapikou A, Polverino E, Ewig S, *et al.* Severity and outcomes of hospitalised community-acquired pneumonia in COPD patients. *Eur Respir J* 2012; 39: 855–861.
61. Molinos L, Clemente MG, Miranda B, *et al.* Community-acquired pneumonia in patients with and without chronic obstructive pulmonary disease. *J Infect* 2009; 58: 417–424.
62. Snijders D, van der Eerden M, de Graaff C, *et al.* The influence of COPD on mortality and severity scoring in community-acquired pneumonia. *Respiration* 2010; 79: 46–53.
63. Pifarre R, Falguera M, Vicente-de-Vera C, *et al.* Characteristics of community-acquired pneumonia in patients with chronic obstructive pulmonary disease. *Respir Med* 2007; 101: 2139–2144.
64. Restrepo MI, Mortensen EM, Pugh JA, *et al.* COPD is associated with increased mortality in patients with community-acquired pneumonia. *Eur Respir J* 2006; 28: 346–351.
65. Rello J, Rodriguez A, Torres A, *et al.* Implications of COPD in patients admitted to the intensive care unit by community-acquired pneumonia. *Eur Respir J* 2006; 27: 1210–1216.
66. Torres A, Dorca J, Zalacaín R, *et al.* Community-acquired pneumonia in chronic obstructive pulmonary disease: a Spanish multicenter study. *Am J Respir Crit Care Med* 1996; 154: 1456–1461.
67. Ruiz M, Ewig S, Marcos MA, *et al.* Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. *Am J Respir Crit Care Med* 1999; 160: 397–405.
68. Marik PE. Pulmonary aspiration syndromes. *Curr Opin Pulm Med* 2011; 17: 148–154.
69. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections – full version. *Clin Microbiol Infect* 2011; 17: Suppl. 6, E1–E59.
70. Bartlett JG, Gorbach SL, Finegold SM. The bacteriology of aspiration pneumonia. *Am J Med* 1974; 56: 202–207.
71. Leroy O, Vandenbussche C, Coffinier C, *et al.* Community-acquired aspiration pneumonia in intensive care units. Epidemiological and prognosis data. *Am J Respir Crit Care Med* 1997; 156: 1922–1929.
72. El-Solh AA, Pietrantoni C, Bhat A, *et al.* Microbiology of severe aspiration pneumonia in institutionalized elderly. *Am J Respir Crit Care Med* 2003; 167: 1650–1654.
73. Torres A, Serra-Batlles J, Ferrer A, *et al.* Severe community-acquired pneumonia. Epidemiology and prognostic factors. *Am Rev Respir Dis* 1991; 144: 312–318.
74. Marrie TJ. Community-acquired pneumonia in the elderly. *Clin Infect Dis* 2000; 31: 1066–1078.
75. Kikuchi R, Watabe N, Konno T, *et al.* High incidence of silent aspiration in elderly patients with community-acquired pneumonia. *Am J Respir Crit Care Med* 1994; 150: 251–253.
76. Teramoto S, Fukuchi Y, Sasaki H, *et al.* High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. *J Am Geriatr Soc* 2008; 56: 577–579.
77. Sekizawa K, Ujiie Y, Itabashi S, *et al.* Lack of cough reflex in aspiration pneumonia. *Lancet* 1990; 335: 1228–1229.
78. Almirall J, Rofes L, Serra-Prat M, *et al.* Oropharyngeal dysphagia is a risk factor for community-acquired pneumonia in the elderly. *Eur Respir J* 2013; 41: 923–928.
79. Lorber B, Swenson RM. Bacteriology of aspiration pneumonia. A prospective study of community- and hospital-acquired cases. *Ann Intern Med* 1974; 81: 329–331.
80. Cesar L, Gonzalez C, Calia FM. Bacteriologic flora of aspiration-induced pulmonary infections. *Arch Intern Med* 1975; 135: 711–714.
81. Bartlett JG, Gorbach SL. Treatment of aspiration pneumonia and primary lung abscess. Penicillin G *vs* clindamycin. *JAMA* 1975; 234: 935–937.
82. Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med* 2001; 344: 665–671.
83. Mier L, Dreyfuss D, Darchy B, *et al.* Is penicillin G an adequate initial treatment for aspiration pneumonia? A prospective evaluation using a protected specimen brush and quantitative cultures. *Intensive Care Med* 1993; 19: 279–284.

84. Marik PE, Careau P. The role of anaerobes in patients with ventilator-associated pneumonia and aspiration pneumonia: a prospective study. *Chest* 1999; 115: 178–183.
85. Fine MJ, Auble TE, Yealy DM, *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336: 243–250.
86. Lim WS, Macfarlane JT, Boswell TC, *et al.* Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. *Thorax* 2001; 56: 296–301.
87. Lim WS, van der Eerden MM, Laing R, *et al.* Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003; 58: 377–382.
88. Ewig S, Torres A. Severity scores for CAP. ''Much workload for the next bias.''. *Thorax* 2010; 65: 853–855.
89. Arancibia F, Bauer TT, Ewig S, *et al.* Community-acquired pneumonia due to gram-negative bacteria and *Pseudomonas aeruginosa*: incidence, risk, and prognosis. *Arch Intern Med* 2002; 162: 1849–1858.
90. Falguera M, Carratalà J, Ruiz-Gonzalez A, *et al.* Risk factors and outcome of community-acquired pneumonia due to Gram-negative bacilli. *Respirology* 2009; 14: 105–111.
91. Meehan TP, Fine MJ, Krumholz HM, *et al.* Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA* 1997; 278: 2080–2084.
92. Dellinger RP, Levy MM, Rhodes A, *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; 39: 165–228.

Chapter 9

Lower respiratory tract infections and adult CAP in primary care

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SUMMARY: Diagnosing community-acquired pneumonia within time-pressured consultations in primary care is challenging. The traditional tools of history and examination poorly predict the presence of radiographic pneumonia. Point-of-care testing with biomarkers, such as C-reactive protein, is feasible and cost-effective, and may help clinicians to better target antibiotic prescription to those who will receive meaningful benefit, thus limiting overuse in those who are unlikely to benefit. Widespread use of antibiotics in primary care for respiratory tract infections is driving antimicrobial resistance and strategies, *e.g.* the use of enhanced communication skills by clinicians has proved effective in safely reducing antibiotic prescribing. Most patients with community-acquired pneumonia can be successfully managed in the community, with antibiotics prescribed according to national guidelines. Assessment of patients who require referral to secondary care can be aided by using severity of illness tools, such as CRB65 (confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, blood pressure $<$90 mmHg (systolic) or $\leqslant$60 mmHg (diastolic), age $\geqslant$65 years), which measure perturbations in simple physiological measures and antibiotic treatment targeted accordingly.

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Respiratory tract infections remain the most frequently encountered acute illness in primary care, with 25% of individuals consulting their general practitioner during the course of 1 year [1, 2], and account for more than 50% of all antibiotic prescriptions in the community [3]. However, most respiratory tract infections are self-limiting or predominantly viral, especially those primarily affecting the upper respiratory tract where antibiotics confer little, if any, benefit [1, 4]. Community-acquired pneumonia (CAP) is often considered a predominantly bacterial disease that may require hospitalisation in some individuals, and is associated with serious complications such as respiratory failure, severe sepsis, multi-organ failure and death [5]. The emergence of both a novel strain of influenza (influenza A (H1N1) pdm09) in 2009 and other unique viruses in the past decade has challenged this view [6–9], and presents a new and emerging threat for primary care physicians.

The cornerstone of managing CAP in the community remains the establishment of a correct diagnosis evaluating the potential benefit and harm of antibiotic treatment, and, when indicated, prescribing an appropriate choice, dose and duration of treatment according to national guidelines, taking local epidemiology into account. Although the majority of patients can be successfully managed in the community and adverse sequelae of CAP are uncommon, there has been an increasing trend in the number of both patients hospitalised with CAP and subsequent admission to critical care [5, 10]. This observation highlights the importance of assessing the potential severity of illness, particularly in an ageing population with a growing number of comorbidities, and timely referral to secondary care. Primary care physicians also need to be cognisant of both seasonal trends and resistance patterns in respiratory pathogens through surveillance programmes. This chapter discusses the diagnosis and management of CAP in primary care in resource rich countries, with a focus on strategies for the safe avoidance of inappropriate antibiotics.

The pros and cons of antibiotic therapy in respiratory tract infections

In Europe, 90–95% of antibiotic courses are prescribed in primary care [11]. Treatment of respiratory tract infections represents the largest single indication, with as many as two-thirds of consultations for a respiratory tract infection resulting in a prescription [3]. The minority of respiratory tract infections in the community are accounted for by pneumonia (approximately 5%) and antibiotics confer little benefit in the remainder [1, 4]. LITTLE *et al.* [4] randomised over 2000 adults with lower respiratory tract infection (LRTI) in whom pneumonia was not suspected to be treated with either amoxicillin (1 g three times a day for 1 week) or placebo. Antibiotic treatment did not reduce severity or duration of symptoms, even in those aged greater than 60 years, but was associated with increased incidence of nausea, rash and diarrhoea (number needed to harm=21, 95% CI 1.1–1.74; p=0.025). However, chest radiographs were taken within 7 days of first consultation (and preferably within 3 days), and approximately 5% were found to have evidence of CAP. Those with CAP who were randomised to treatment with amoxicillin had a shorter duration of "moderately bad" symptoms compared to those with CAP treated with placebo [4]. Importantly, in this cohort of 2061 patients with LRTI in whom CAP was not suspected, only three patients (two randomised to placebo, one to amoxicillin) were admitted to hospital and there were no deaths. In a retrospective study of a UK primary care database, MEROPOL *et al.* [3] examined 1 531 019 patients presenting with acute respiratory tract infections, of whom 65% were treated with an antibiotic for hospitalisation for an adverse drug event (hypersensitivity, diarrhoea, seizure, arrhythmia, hepatic or renal failure) or CAP. There was no significant difference in the number of adverse events and CAP. The adjusted risk for admission with CAP was significantly reduced; however, the number needed to treat of patients in primary care with respiratory tract infections in order to prevent one hospital admission with CAP was 12 255. Consequently, the widespread use of antibiotics for respiratory infections in primary care is of little benefit in the majority of cases, but is associated with the development of antibiotic resistance [12, 13].

The emergence of multidrug-resistant organisms in the absence of new antimicrobial drugs threatens a return to the pre-antibiotic era and results in prolonged illness, treatment failure, increased healthcare costs and risk of death. The World Health Organization has highlighted antimicrobial resistance as a major threat to global health and economic growth. In an observational paediatric cohort study of acute respiratory infections, the minimum inhibitory concentration for ampicillin tripled (9.2 $\mu g \cdot mL^{-1}$ *versus* 2.7 $\mu g \cdot mL^{-1}$; p=0.005) and the number of *Haemophilus* spp. isolates with the conjugative resistance element ICEHin1056 doubled (67% *versus* 36%; relative risk 1.9, 95% CI 1.2–2.9) within 2 weeks of antibiotic therapy [12]. A systematic review and meta-analysis by COSTELLOE *et al.* [13] identified seven studies of respiratory tract bacteria in which the odds ratio for antibiotic resistance was 2.4 (95% CI 1.3–4.5) at 12 months.

Multiple courses and longer periods of treatment increased the risk of resistance [13]. The widespread use of antibiotics in the community and their effects on microbial ecology means that resistant organisms previously only associated with hospitalised patients are now seen in patients presenting to primary care [14–16]. Infections with resistant organisms are symptomatic for longer and are associated with an increased burden on the health services compared to infections with sensitive organisms, even in primary care [17, 18].

In the pre-antibiotic era, mortality from CAP was approximately 20% increasing to 60% in patients with bacteraemia [19]. There have been no trials comparing antibiotic therapy with placebo for CAP. Patients with CAP may survive if antimicrobials are not administered [19, 20], and may even recover at the same rate, suggesting that patients not requiring admission to hospital may not always be harmed if they are not treated with antibiotics [20]. However, in hospitalised patients with more severe CAP, a delay in appropriate therapy is associated with increased mortality [21]. Despite the uncertainty expressed by some clinicians as to whether all CAP patients should be treated with antibiotics, the British Thoracic Society guidelines recommend that antimicrobial drugs are always indicated when a diagnosis of CAP is made [22].

Does this patient have CAP?

Acute respiratory infection is the most common reason for presentation to general practitioners; therefore, it is important that clinicians can differentiate patients with CAP from other respiratory tract infections, as management differs between the two populations [1, 2]. Delayed antibiotic therapy for CAP may be associated with increased mortality [21, 23], whilst erroneous diagnosis leads to inappropriate antibiotic use and incorrect therapy for alternative diagnoses. CAP also imposes a substantial economic burden [24–27]. Although the majority of direct healthcare costs are attributed to secondary care [24–27], particularly those greater than 65 years of age [28]; most of the economic impact is accounted for by lost days of work. In the USA, the estimated cost of CAP is more than $17 billion [25], whilst in Europe it is approximately €10.1 billion per annum [24]. The latter is attributed to approximately €500 million in the community and €5.7 billion to secondary care, while the majority of the remaining costs are as a result of absence from work [24]. Correctly diagnosing CAP, assessing whether the patient requires antibiotics and/or referral to hospital has to be completed in a relatively short timeframe [29], with little opportunity for obtaining contemporaneous diagnostic investigations such as a chest radiograph. Accordingly, diagnosing and managing CAP in the community is often clinically challenging.

The rational clinical examination

The gold standard for diagnosing CAP is the presence of a chest radiograph demonstrating new consolidation in a patient with a history and examination findings consistent with CAP. However, chest radiography is inadequate as infiltrates may develop up to 48 h after the onset of symptoms [30], and abnormalities can be demonstrated with computed tomography, even in the presence of a normal chest radiograph [31]. Routine chest radiography for LRTI in general practice is not feasible and is unlikely to be cost effective. Consequently, the history and clinical examination must strongly influence which patients should have chest radiography, and which to refer for assessment in hospital. However, on the basis of clinical parameters alone, diagnostic accuracy is poor and clinicians will often over diagnose CAP prior to the results of a chest radiograph being available, or miss the diagnosis altogether [32–34]. Typical symptoms of CAP include dyspnoea, chest pain, productive cough, rigours and confusion; the latter may be the predominant feature in the elderly. Systemic features may predominate, with a clinical picture of sepsis or septic shock, with few symptoms and signs pointing to chest infection. Individual symptoms are often nonspecific and the differential diagnosis includes asthma, chronic obstructive pulmonary disease (COPD), pulmonary oedema or embolus, neoplasia, interstitial lung disease including organising pneumonia, bronchiectasis, bronchitis, rhinosinusitis and pharyngitis [32]. The history should

focus on known risk factors for CAP such as smoking, overcrowding, contact with other CAP patients, pets, excessive alcohol, dysphagia, drugs such as steroids, acid suppression or sedatives [35–40]. Studies have investigated whether the presence or absence of specific symptoms are predictive of CAP [41–44]. Individual symptoms have a poor predictive value, which is unsurprising when one considers these symptoms are common to many cardiorespiratory diseases. Patient consultation is a complex process and eliciting a history requires training, experience and skill [45]. Medical history taking therefore remains the focal point of constructing a differential diagnosis.

In a prospective study of 252 febrile patients with respiratory tract infection in primary care clinics, university hospital clinicians were asked to judge whether patients had pneumonia on clinical grounds and their diagnoses were compared to chest radiograph findings [46]. The ability to predict pneumonia on the basis of history and examination had a positive predictive value of only 27% compared to a radiograph, but the negative predictive value was 97%. In a single centre, retrospective study of patients admitted to hospital with CAP before and after the Infectious Diseases Society of America guidelines recommended the initiation of antibiotic therapy within 4 h of hospitalisation, KANWAR *et al.* [47] examined the time to antibiotic administration and final diagnosis. Following the introduction of the guidelines in 2003, more patients were diagnosed with CAP and given antibiotics within 4 hours (65.8% *versus* 53.8%), but significantly fewer patients were finally diagnosed with CAP on chest radiography (58.9% in 2005 from 75.9% in 2003, $p<0.001$). More recently, VAN VUGT *et al.* [48] investigated accuracy of primary care physicians' clinical diagnoses in 2810 patients presenting with acute cough in 12 countries. Clinicians recorded whether they considered the patient had pneumonia and a blinded radiologist reported on the findings of the chest radiograph taken within 7 days of first presentation. 140 (5%) patients had radiological evidence of pneumonia, of whom 41 (29%) were identified by the general practitioner. In total, 72 patients were diagnosed clinically as having pneumonia which represented a positive predictive value of 57%. Negative predictive value, sensitivity and specificity of the clinician's judgment were 96%, 29% and 99%, respectively. The accuracy of physical examination of the chest alone using auscultation, palpation and percussion in diagnosing pneumonia was investigated in 24 patients with and 28 patients without radiographic evidence of CAP and interobserver reliability was assessed amongst three experienced examiners [49]. The presence of unilateral crackles was the most useful examination finding but sensitivity, specificity and interobserver agreement were poor.

In summary, medical history and clinical examination are the tools most commonly available in general practice to identify patients at high risk for CAP and to initiate antibiotic therapy. However, there is weak agreement between clinicians' diagnoses, and the predictive value of clinical diagnoses is poor. Because more serious CAP presenting in general practice is rare, we do not know how well general practitioner diagnosis performs in correctly identifying these cases. However, it is likely to be better than the in the study by VAN VUGT *et al.* [48] because patients with more serious pneumonia are unlikely to have been included in that study. Improving the accuracy of CAP diagnosis requires alternative strategies which may include clinical decision tools, alternative imaging modalities or use of point-of-care tests with higher negative and positive predictive values, as obtaining a chest radiograph at the consultation is not feasible in all areas of community practice [50].

Improving diagnostic accuracy with point-of-care testing using biomarkers: C-reactive protein

A number of commercial point-of-care tests are now available and can display diagnostic information in less than 4 min, making this technology potentially widely applicable to time-pressured consultations in general practice. The most studied and widely used point-of-care test is C-reactive protein (CRP), an acute-phase protein that rapidly increases during acute inflammation and can be measured in 3–4 min using blood from a finger prick test [51]. It costs approximately

€4 per investigation [52]. Two systematic reviews have examined the role of CRP in primary care LRTIs [52, 53]. VAN DER MEER *et al.* [53] assessed the diagnostic accuracy of CRP in radiologically proven pneumonia and concluded that the studies undertaken at that time were of poor quality and that the results suggested that CRP was not sensitive enough to rule out or specific enough to rule in infiltrates on a radiograph. More recently, ENGEL *et al.* [52] reviewed the evidence for CRP guiding antibiotic prescription and diagnosis of CAP. In total, 13 studies of variable quality were identified and the authors concluded that the evidence for the benefits of measuring CRP in primary care were limited, contradictory and did not support its use in guiding management decisions. CALS *et al.* [54] performed a randomised clinical trial in patients with a LRTI or rhinosinusitis in the Netherlands using CRP levels to guide antibiotic prescription. Patients randomised to having CRP measured had fewer antibiotic prescriptions at the first consultation and delayed prescriptions (*i.e.* patients were given a prescription and told to get the antibiotics if they didn't get better) were less often filled as the patient collected the prescription from the pharmacy.

Additional studies have incorporated CRP point-of-care testing with other aspects of the clinical consultation. In a pragmatic, 2×2 factorial, cluster-randomised clinical trial in the Netherlands an illness- or disease-specific intervention effect was assessed on antibiotic prescriptions for LRTIs [55]. The disease-specific intervention involved point-of-care CRP testing, whilst the illness-specific intervention involved training practitioners in enhanced communication skills. The latter is a patient-centred approach focussing on the whole patient cohort and shared decision making, and includes elements such as exploring patients' expectations and fears or opinions on antibiotics. Antibiotics were prescribed to 31% of the patients in the CRP group compared to 53% in the non-CRP testing cohort ($p=0.02$). Clinicians trained in enhanced communication skills prescribed antibiotics to 27% compared to 54% in the untrained group ($p<0.01$). In the combined intervention group, antibiotics were given to only 23%, although there was no statistically significant synergistic effect of the two interventions. An economic evaluation of this trial demonstrated that both interventions were cost-effective [56]. Follow-up of the same cohort of patients 3.5 years later showed that clinicians trained in enhanced communication skills treated 26.1% of all subsequent respiratory tract infections in trial patients with antibiotics compared to 39.1% by untrained practitioners ($p=0.02$) [57]. In a subsequent study using Internet-based training in 246 practices in six European countries, involving over 11 000 patients, similar results were obtained for prescribing in acute respiratory infections [58]. Antibiotic prescriptions were lower with CRP training (33% *versus* 48%, adjusted risk ratio (RR) 0.54, 95% CI 0.42–0.69) and enhanced communication training (36% *versus* 45%, adjusted RR 0.69, 95% CI 0.54–0.87). However, in this study, a synergistic effect of CRP and communication skill training was observed with a relative RR of 0.38 (95% CI 0.25–0.55) [58]. A similar study, CHANGE-2, is currently underway in Germany and is a three-armed, cluster-randomised clinical trial comparing communication training and communication training with CRP testing *versus* standard care [59]. The study will recruit 188 primary care physicians and is expected to include more than 13 000 patients over a 3-year period.

Alternative biomarkers in point-of-care testing

Procalcitonin

Procalcitonin is a pro-hormone that is elevated during acute bacterial infections and has been evaluated in several primary care studies. BRIEL *et al.* [60] studied 53 primary care physicians who recruited 458 patients with a respiratory tract infection in whom they wished to prescribe antibiotics according to guidelines. 50% of the patients were randomised to having their procalcitonin level rapidly measured at a local hospital and antibiotics were recommended if the level was greater than 0.25 $\mu g \cdot L^{-1}$ or discouraged if the level was below 0.25 $\mu g \cdot L^{-1}$. If antibiotics were not prescribed, procalcitonin was measured again within 24 h and antibiotics were prescribed if the either the level was greater than 0.25 $\mu g \cdot L^{-1}$ or there was a 50% increase from baseline. There was no difference between groups in the primary outcome measure or days of

restricted activity from infection, but antibiotics were only prescribed for 25% of the procalcitonin group compared to 97% of controls. However, this result can be put into context by the study of HOLM *et al.* [61] who enrolled 364 patients with LRTI, from 42 general practices, who did not require hospitalisation and who underwent a chest radiograph in addition to measuring CRP, procalcitonin and microbiological sampling. 48 (13%) patients were diagnosed with pneumonia and there was a statistically significant difference between pneumonia and non-pneumonia patients for all cut-off values of procalcitonin. However, at higher cut off values, the specificity and positive predictive value were high but sensitivity decreased to unacceptable levels. Comparison of CRP and procalcitonin evaluated by a receiver operating characteristic (ROC) curve analysis revealed no significant difference in the two tests. In a large study involving more than 2800 patients in 12 European countries, using a clinical decision tool and CRP with a cut-off of 30 $mg \cdot L^{-1}$, the addition of procalcitonin did not provide any additional diagnostic information [62]. Although there is considerable enthusiasm for using procalcitonin to limit antibiotic therapy [63], there are few data supporting its superiority over measuring CRP to aid the diagnosis of CAP and guide antibiotic prescription decisions. Furthermore, although a point-of-care test has now been developed for procalcitonin, it is semi-quantitative and the lower cut-off value exceeds the median value measured in a large primary care cohort [61]. A clinical study validating this assay against laboratory based procalcitonin measurement is yet to commence (www.clinicaltrials.gov identifier NCT01771029).

Pneumococcal antigen

Streptococcus pneumoniae is the causative organism in approximately one-third of patients with CAP. Commercial tests that detect pneumococcal antigen in urine have been available for some time and provide a result within 15 min. A recent meta-analysis of 27 studies concluded that the sensitivity of urine testing was 74% with 97% specificity [64], although the sensitivity is higher in bacteraemia [65]. While urine testing has been used extensively in the hospital setting, it has not been validated for primary care and is generally not advocated in guidelines [22].

Viruses and *Legionella*

Point-of-care tests are also available for a number of other infectious agents including influenza, respiratory syncytial virus and *Legionella*, but are not currently widely used in primary care. Routine microbiological sampling in primary care is generally not recommended by guidelines [22, 66] unless symptoms do not resolve or tuberculosis is suspected [22].

Should patients with CAP be admitted to hospital?

Once a diagnosis of CAP has been made, guidelines recommend that antibiotics should be administered [22]. The pertinent question for the primary care physician remains whether or not the patients should continue to be managed in the community or admitted to hospital. In the UK, approximately 20% of patients with CAP are admitted to hospital [22], and this decision needs to take into account the patient's severity of illness, comorbidities and risk factors for a poorer outcome, in addition to social factors. Fortunately, severity of illness is characterised by perturbations in a number of simple physiological measures, which can be easily assessed by clinical examination [67]. Guidelines recommend that clinical judgement of the general practitioner may be supplemented by severity assessment tools [22]. In primary care, the simplest and most practically applied severity assessment tool is CRB65 (tables 1 and 2), which is used to predict 30-day mortality in CAP patients [68, 69]. This tool uses a single point for the presence of confusion, age greater than 65 years, and abnormalities in respiratory rate and blood pressure to stratify patients into risk groups. Alternative severity assessment tools, such as CURB (confusion, urea >7 $mmol \cdot L^{-1}$, respiratory rate $\geqslant 30$ $breaths \cdot min^{-1}$, blood pressure <90 mmHg (systolic) or $\leqslant 60$ mmHg (diastolic)), CURB65 (CURB plus age $\geqslant 65$ years) and the Pneumonia Severity Index (PSI), all perform well but have the disadvantage of incorporating laboratory measurements that are frequently unavailable at the first consultation in primary practice [69].

Table 1. CRB65 severity assessment tool

Score one point for each of the following
C: confusion (acute)
R: respiratory rate $\geqslant$30 breaths·min^{-1}
B: blood pressure $<$90 mmHg systolic or $\leqslant$60 mmHg diastolic
65: age $\geqslant$65 years

One needs to be aware that CRB65 originated to describe 30-day mortality in patients admitted to hospital with CAP, rather than being derived from patients in the community with CAP, some of whom may have been admitted to hospital, and this may be a limitation of this tool. Furthermore, as CRB65 uses parameters with a threshold, it is likely to be insensitive in many patients and, here, the clinician's experience becomes of paramount importance. Two studies have explored the use and validity of CRB65 in primary care. In a Dutch study, BONT *et al.* [70] prospectively included 315 patients greater than 65 years of age (mean 77.3 years) with a diagnosis of pneumonia on the basis of new localising chest signs, new infiltrates on a chest radiograph or a strong clinical suspicion in a severely ill patient. The CRB65 score performed similarly to the original description in hospitalised patients in predicting 30-day mortality [68]. Patients with a score of 1 (all $\geqslant$65) had a mortality of 0.9%, increasing to 11% for a score of 2 or higher. FRANCIS *et al.* [71] prospectively studied patients with an acute or deteriorating cough suggestive of a LRTI in 14 primary care networks in 13 European countries. Confusion and age data were recorded for almost all of the 3368 patients but respiratory rate (22.7%) and blood pressure (31.9%) were recorded infrequently, and the CRB65 score could only be determined in 12.6% of this cohort. Only 12 patients with a clinical diagnosis of CAP had a complete CRB65 score.

In practice, many CAP patients suitable for ambulatory care in the community because of a low severity assessment score are in fact admitted to hospital [72, 73]. A British Thoracic Society audit undertaken in 2009/2010 included 2749 CAP patients in 64 hospitals and found that 40% of inpatients had a CURB65 score of 0 or 1 [72]. LABARERE *et al.* [73] used the PSI to identify low-risk patients in 32 emergency departments and found that 44.7% were admitted. In approximately 80% of the PSI-classified low-risk patients, additional factors were identified such as medical or psychosocial contraindications to outpatient therapy, comorbid conditions not encompassed by PSI such as cognitive impairment, ischaemic heart disease, diabetes, chronic lung disease, or home oxygen therapy [73].

Pulse oximetry is a simple, noninvasive method for assessing oxygenation and has been used for many years within hospitals, but has been used infrequently in general practice [74]. An arterial oxygen saturation (S_aO_2) $<$90% is associated with adverse outcomes in hospitalised patients (relative risk of death associated with desaturation was 3.3, 95% CI 1.41–8.2) and the need for oxygen therapy [75]. Delays in measuring oxygen saturation in hospitalised patients are associated with delayed antibiotic therapy and increased risk of death [76]. Pulse oximetry is recommended as part of the severity assessment in British Thoracic Society guidelines on CAP [22], in addition to asthma and COPD, but is used by only around one-fifth of general practitioners in the UK [75]. BEWICK *et al.* [77] prospectively studied a cohort of 832 patients admitted to a single UK hospital with CAP (467 had S_aO_2 measured on air) and concluded that oxygen saturations $<$90% on air

Table 2. The triage decision should be made according to the CRB65 score

Severity	Score	Decision
Low	0	Appropriate for home treatment and oral antibiotics
Moderate	1–2	Consider hospital referral
High	3–4	Urgent hospital referral with a view to admission and empirical antibiotics

Patient's psychosocial circumstances and comorbidities should also be taken into consideration. CRB65: confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, blood pressure $<$90 mmHg (systolic) or $\leqslant$60 mmHg (diastolic), age $\geqslant$65 years.

had a good specificity (76%) but poor sensitivity (46%) for 30-day mortality. The area under the curve of the ROC curve for CRB65 predicting 30-day mortality was not improved by adding oxygen saturations. However, mortality or admission to critical care was 48.8% in patients with CRB65 scores of 0 or 1 and SaO_2 <90%. This illustrates one limitation of the CRB65 tool and emphasises the importance of clinicians' clinical judgement in assessing patients [22]. As this cohort investigated patients admitted to hospital with CAP and represents only one-fifth of patients managed by primary care physicians, results must be interpreted with caution [77]. Nevertheless, an observation of SaO_2 <90% may be a useful adjunct in identifying illness severity in patients with low CRB65 scores. A primary care evaluation of the diagnostic utility of SaO_2 for CAP is needed.

Antibiotic resistance and CAP

The widespread use of antibiotics in primary care is associated with the selection and emergence of antibiotic resistance [12, 13]. In a recent report from Barcelona, Spain, and Edinburgh, UK, the prevalence of multidrug-resistant pathogens causing CAP was 7.6% and 3.3%, respectively, of which the commonest organisms were methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* [78]. Drug resistance has important consequences for individual patients as initial empirical therapy is likely to be less effective, leading to treatment failure and higher morbidity in those infected with a resistant organism. Echoing a UK study [79], a qualitative interview study of 80 primary care physicians in nine countries found that most clinicians did not consider antimicrobial resistance to be an important problem in their own practice [80], and often viewed antibiotic treatment failure as a consequence of a viral aetiology rather than linking it to their own prescribing [81]. There is a wide variation in the prescription of antibiotics across European countries [82] and in the community for LRTI [83], which may be related to both clinical [84] and non-clinical factors such as patient access to over the counter medicines, patient expectations for antibiotics, lack of consistent guidelines and belief in shared decision making [85]. Concordance with guidelines is often poor with only a minority of patients in one large European study receiving first-choice antibiotics [86].

Antibiotic prescriptions are also more likely when there is an expectation from patients that an antibiotic will be prescribed [87]. Training in enhanced consultation skills that incorporate patients' beliefs on antibiotics, expectations and an explanation on the expected course of the respiratory illness is as effective as point-of-care testing with CRP at reducing antibiotic prescriptions [55], and reduces subsequent prescribing for patients presenting with the same symptoms [57]. Enhanced consultation skills may also be delivered through Internet-based training across educational and cultural barriers [58], or blended learning interventions [88, 89].

Prevention

Cigarette smoking is a risk factor for CAP and smoking cessation interventions should be offered to all smokers diagnosed with CAP [22]. Pneumonia and invasive pneumococcal disease may be prevented by pneumococcal polysaccharide vaccination. In the UK this is recommended for adults over the age of 65 years and those at high risk under the age of 65 years. The latter includes chronic respiratory, cardiac, renal and liver disease, asplenia, diabetes, immunosuppression, and cerebrospinal fluid leaks. European guidelines offer similar advice but also include previous pneumonia, institutionalisation and dementia as risk factors [66]. Vaccination against seasonal influenza is recommended in a similar cohort of patients and general practitioners can facilitate vaccination uptake by having an up-to-date register of those aged greater than or less than 65 years who are at risk. Poor oral health is being increasingly recognised as a risk factor in CAP and patients should be encouraged to regularly attendant dental appointments [35].

The future of managing CAP in the community

Lung ultrasound

This imaging modality may confer several advantages over chest radiography in that small portable devices are now widely available, allowing ultrasound to be performed as part of the clinical examination [90]. This technique can also be quickly and reliably taught to non-radiologists [91]. Lung ultrasound has not been evaluated in a primary care setting although several studies have appraised this modality in the diagnosis of CAP in other contexts. REISSIG *et al.* [92] conducted a prospective multicentre study of ultrasound to diagnose CAP in 14 European centres. History, clinical examination, laboratory tests and ultrasound were performed in 362 patients with suspected CAP. A chest radiograph in two planes was taken and if the radiograph was inconclusive or negative with an abnormal ultrasound, then a low-dose CT scan was performed. CAP was confirmed in 229 (63%) patients and lung ultrasound had a sensitivity of 93.4% (95% CI 89.2–96.3%), specificity of 97.7% (95% CI 93.4–99.6%), and likelihood ratios of 40.5 (95% CI 13.2–123.9) for positive and 0.07 (95% CI 0.04–0.11) for negative results [92]. Addition of auscultation improved likelihood ratios further. Typical ultrasound findings included infiltrates (97.6%), air bronchograms (87.6%) and pleural effusions (54.4%). Comparing lung ultrasound to radiographic findings, 26 cases of ultrasound-detected CAP were missed or equivocal by radiography, whereas chest radiography detected 14 cases that were missed by lung ultrasound [92]. Similar results have been obtained in other studies including children and adults where ultrasound has often been superior to chest radiographs [91, 93–96]. In a prospective observational study in two emergency departments, clinicians were given 1 h of focussed training in lung ultrasound [91]. 200 patients up to the age of 21 years were examined and ultrasound had an overall sensitivity of 86% (95% CI 71–94%) and specificity of 89% (95% CI 83–93%). In a case series of 20 patients during the 2009 influenza pandemic, ultrasound distinguished viral from bacterial pneumonia with high interobserver agreement [97], and detected viral pneumonia in the presence of normal chest radiographs [98]. Lung ultrasound may also be used to reliably estimate lung water and, therefore, may rule in or rule out pulmonary oedema from the differential diagnosis [99].

Antibiotic dosing and duration

Specific antibiotic therapy depends on resistance patterns and local or national guidelines [22, 66], therefore it has not been covered in this chapter. Patients who are managed in the community may be treated with oral antibiotics for a duration of approximately 7 days if the patient demonstrates signs of improvement [22, 66]. Clinical deterioration should prompt the clinician to consider whether the diagnosis of CAP is correct, a complication such as empyema or lung abscess has developed, or the organism is resistant to the antibiotic chosen. Duration of therapy for uncomplicated CAP has been addressed in a number of studies and systematic reviews [100, 101]. Shorter courses of antibiotics are likely to increase compliance and minimise the emergence of resistance. Antibiotic therapy of 5 days or less appears to be as effective as courses of 7 days or more [101]. Procalcitonin may be used to limit the duration of therapy without harm [102, 103]. Exactly how short antibiotic regimens can be in uncomplicated CAP treated in the community remains to be elucidated. Duration of therapy and investigation of dose in relation to pharmacokinetics and pharmacodynamics are likely to be important areas of future research in order to better tailor antibiotic therapy, maximise benefit to individual patients, and help contain antimicrobial resistance [104].

Conclusions

Diagnosing CAP in primary care is challenging. Significant progress had been made in understanding the rationale for the observed high rates and variability in antibiotic prescribing.

To date, clinicians in primary care have been hampered by imperfect tools to both diagnose and assess patients with CAP. A number of point-of-care investigations may improve this process but require further evaluation in a community setting.

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References

1. National Institute for Health and Care Excellence. Respiratory tract infections – antibiotic prescribing: prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. NICE clinical guideline 69. London, NICE, 2008.
2. Ashworth M, Charlton J, Ballard K, *et al.* Variations in antibiotic prescribing and consultation rates for acute respiratory infection in UK general practices 1995–2000. *Br J Gen Pract* 2005; 55: 603–608.
3. Meropol SB, Localio AR, Metlay JP. Risks and benefits associated with antibiotic use for acute respiratory infections: a cohort study. *Ann Fam Med* 2013; 11: 165–172.
4. Little P, Stuart B, Moore M, *et al.* Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. *Lancet Infect Dis* 2013; 13: 123–129.
5. Woodhead M, Welch CA, Harrison DA, *et al.* Community-acquired pneumonia on the intensive care unit: secondary analysis of 17,869 cases in the ICNARC Case Mix Programme Database. *Crit Care* 2006; 10: Suppl. 2, S1.
6. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, Dawood FS, Jain S, *et al.* Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009; 360: 2605–2615.
7. Zaki AM, van Boheemen S, Bestebroer TM, *et al.* Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012; 367: 1814–1820.
8. Ksiazek TG, Erdman D, Goldsmith CS, *et al.* A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003; 348: 1953–1966.
9. Gao R, Cao B, Hu Y, *et al.* Human infection with a novel avian-origin influenza A (H7N9) virus. *N Engl J Med* 2013; 368: 1888–1897.
10. Trotter CL, Stuart JM, George R, *et al.* Increasing hospital admissions for pneumonia, England. *Emerg Infect Dis* 2008; 14: 727–733.
11. Vander Stichele RH, Elseviers MM, Ferech M, *et al.* Hospital consumption of antibiotics in 15 European countries: results of the ESAC Retrospective Data Collection (1997–2002). *J Antimicrob Chemother* 2006; 58: 159–167.
12. Chung A, Perera R, Brueggemann AB, *et al.* Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study. *BMJ* 2007; 335: 429.
13. Costelloe C, Metcalfe C, Lovering A, *et al.* Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010; 340: c2096.
14. Wunderink RG. How important is methicillin-resistant *Staphylococcus aureus* as a cause of community-acquired pneumonia and what is best antimicrobial therapy? *Infect Dis Clin North Am* 2013; 27: 177–188.
15. Jung WJ, Kang YA, Park MS, *et al.* Prediction of methicillin-resistant *Staphylococcus aureus* in patients with non-nosocomial pneumonia. *BMC Infect Dis* 2013; 13: 370.
16. Lobo LJ, Reed KD, Wunderink RG. Expanded clinical presentation of community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia. *Chest* 2010; 138: 130–136.
17. Alam MF, Cohen D, Butler C, *et al.* The additional costs of antibiotics and re-consultations for antibiotic-resistant *Escherichia coli* urinary tract infections managed in general practice. *Int J Antimicrob Agents* 2009; 33: 255–257.
18. Butler CC, Hillier S, Roberts Z, *et al.* Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload: outcomes for patients with *E. coli* UTIs. *Br J Gen Pract* 2006; 56: 686–692.
19. Bullowa JG. Pneumonia due to pneumococcus type XIV (Cooper) and its treatment with specific antiserum. *J Clin Invest* 1935; 14: 373–383.
20. Hopstaken RM, Coenen S, Butler CC. Treating patients not diagnoses: challenging assumptions underlying the investigation and management of LRTI in general practice. *J Antimicrob Chemother* 2005; 56: 941–943.

21. Garnacho-Montero J, García-Cabrera E, Diaz-Martín A, *et al.* Determinants of outcome in patients with bacteraemic pneumococcal pneumonia: importance of early adequate treatment. *Scand J Infect Dis* 2010; 42: 185–192.
22. Levy ML, Le Jeune I, Woodhead MA, *et al.* Primary care summary of the British Thoracic Society Guidelines for the management of community acquired pneumonia in adults: 2009 update. Endorsed by the Royal College of General Practitioners and the Primary Care Respiratory Society UK. *Prim Care Respir J* 2010; 19: 21–27.
23. Meehan TP, Fine MJ, Krumholz HM, *et al.* Quality of care, process, and outcomes in elderly patients with pneumonia. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA* 1997; 278: 2080–2084.
24. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax* 2012; 67: 71–79.
25. File TM Jr, Marrie TJ. Burden of community-acquired pneumonia in North American adults. *Postgrad Med* 2010; 122: 130–141.
26. Raut M, Schein J, Mody S, *et al.* Estimating the economic impact of a half-day reduction in length of hospital stay among patients with community-acquired pneumonia in the US. *Curr Med Res Opin* 2009; 25: 2151–2157.
27. Guest JF, Morris A. Community-acquired pneumonia: the annual cost to the National Health Service in the UK. *Eur Respir J* 1997; 10: 1530–1534.
28. Monge V, San-Martín VM, González A. The burden of community-acquired pneumonia in Spain. *Eur J Public Health* 2001; 11: 362–364.
29. Irving G, Reeve J. Do GPs really provide 47 minutes a year for the patient? *Br J Gen Pract* 2012; 62: 404–405.
30. Hagaman JT, Rouan GW, Shipley RT, *et al.* Admission chest radiograph lacks sensitivity in the diagnosis of community-acquired pneumonia. *Am J Med Sci* 2009; 337: 236–240.
31. Syrjälä H, Broas M, Suramo I, *et al.* High-resolution computed tomography for the diagnosis of community-acquired pneumonia. *Clin Infect Dis* 1998; 27: 358–363.
32. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *JAMA* 1997; 278: 1440–1445.
33. Metlay JP, Fine MJ. Testing strategies in the initial management of patients with community-acquired pneumonia. *Ann Intern Med* 2003; 138: 109–118.
34. Singh H, Giardina TD, Meyer AN, *et al.* Types and origins of diagnostic errors in primary care settings. *JAMA Intern Med* 2013; 173: 418–425.
35. Almirall J, Bolíbar I, Serra-Prat M, *et al.* New evidence of risk factors for community-acquired pneumonia: a population-based study. *Eur Respir J* 2008; 31: 1274–1284.
36. Dublin S, Walker RL, Jackson ML, *et al.* Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study. *J Am Geriatr Soc* 2011; 59: 1899–1907.
37. Eom CS, Jeon CY, Lim JW, *et al.* Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *CMAJ* 2011; 183: 310–319.
38. Almirall J, González CA, Balanzó X, *et al.* Proportion of community-acquired pneumonia cases attributable to tobacco smoking. *Chest* 1999; 116: 375–379.
39. Almirall J, Bolíbar I, Serra-Prat M, *et al.* Inhaled drugs as risk factors for community-acquired pneumonia. *Eur Respir J* 2010; 36: 1080–1087.
40. Almirall J, Rofes L, Serra-Prat M, *et al.* Oropharyngeal dysphagia is a risk factor for community-acquired pneumonia in the elderly. *Eur Respir J* 2013; 41: 923–928.
41. Graffelman AW, le Cessie S, Knuistingh Neven A, *et al.* Can history and exam alone reliably predict pneumonia? *J Fam Pract* 2007; 56: 465–470.
42. Hopstaken RM, Muris JW, Knottnerus JA, *et al.* Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection. *Br J Gen Pract* 2003; 53: 358–364.
43. Melbye H, Straume B, Aasebø U, *et al.* The diagnosis of adult pneumonia in general practice. The diagnostic value of history, physical examination and some blood tests. *Scand J Prim Health Care* 1988; 6: 111–117.
44. Heckerling PS, Tape TG, Wigton RS, *et al.* Clinical prediction rule for pulmonary infiltrates. *Ann Intern Med* 1990; 113: 664–670.
45. Jiwa M. The business of doctoring. *Australas Med J* 2012; 5: 329–333.
46. Lieberman D, Shvartzman P, Korsonsky I, *et al.* Diagnosis of ambulatory community-acquired pneumonia. Comparison of clinical assessment *versus* chest X-ray. *Scand J Prim Health Care* 2003; 21: 57–60.
47. Kanwar M, Brar N, Khatib R, *et al.* Misdiagnosis of community-acquired pneumonia and inappropriate utilization of antibiotics: side effects of the 4-hour antibiotic administration rule. *Chest* 2007; 131: 1865–1869.
48. Van Vugt SF, Verheij T, Jong PD, *et al.* Diagnosing pneumonia in patients with acute cough: clinical judgment compared to chest radiography. *Eur Respir J* 2013; 42: 1076–1082.
49. Wipf JE, Lipsky BA, Hirschmann JV, *et al.* Diagnosing pneumonia by physical examination: relevant or relic? *Arch Intern Med* 1999; 159: 1082–1087.
50. Melbye H. Community pneumonia – more help is needed to diagnose and assess severity. *Br J Gen Pract* 2002; 52: 886–888.

51. Seamark DA, Backhouse SN, Powell R. Field-testing and validation in a primary care setting of a point-of-care test for C-reactive protein. *Ann Clin Biochem* 2003; 40: 178–180.
52. Engel MF, Paling FP, Hoepelman AI, *et al.* Evaluating the evidence for the implementation of C-reactive protein measurement in adult patients with suspected lower respiratory tract infection in primary care: a systematic review. *Fam Pract* 2012; 29: 383–393.
53. van der Meer V, Neven AK, van den Broek PJ, *et al.* Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. *BMJ* 2005; 331: 26.
54. Cals JW, Schot MJ, de Jong SA, *et al.* Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. *Ann Fam Med* 2010; 8: 124–133.
55. Cals JW, Butler CC, Hopstaken RM, *et al.* Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ* 2009; 338: b1374.
56. Cals JW, Ament AJ, Hood K, *et al.* C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial. *J Eval Clin Pract* 2011; 17: 1059–1069.
57. Cals JW, de Bock L, Beckers PJ, *et al.* Enhanced communication skills and C-reactive protein point-of-care testing for respiratory tract infection: 3.5-year follow-up of a cluster randomized trial. *Ann Fam Med* 2013; 11: 157–164.
58. Little P, Stuart B, Francis N, *et al.* Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. *Lancet* 2013; 328: 1175–1182.
59. Altiner A, Berner R, Diener A, *et al.* Converting habits of antibiotic prescribing for respiratory tract infections in German primary care – the cluster-randomized controlled CHANGE-2 trial. *BMC Fam Pract* 2012; 13: 124.
60. Briel M, Schuetz P, Mueller B, *et al.* Procalcitonin-guided antibiotic use *vs* a standard approach for acute respiratory tract infections in primary care. *Arch Intern Med* 2008; 168: 2000–2007.
61. Holm A, Pedersen SS, Nexoe J, *et al.* Procalcitonin *versus* C-reactive protein for predicting pneumonia in adults with lower respiratory tract infection in primary care. *Br J Gen Pract* 2007; 57: 555–560.
62. van Vugt SF, Broekhuizen BD, Lammens C, *et al.* Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough: diagnostic study. *BMJ* 2013; 346: f2450.
63. Schuetz P, Briel M, Mueller B. Clinical outcomes associated with procalcitonin algorithms to guide antibiotic therapy in respiratory tract infections. *JAMA* 2013; 309: 717–718.
64. Sinclair A, Xie X, Teltscher M, *et al.* Systematic review and meta-analysis of a urine-based pneumococcal antigen test for diagnosis of community-acquired pneumonia caused by *Streptococcus pneumoniae. J Clin Microbiol* 2013; 51: 2303–2310.
65. Smith MD, Sheppard CL, Hogan A, *et al.* Diagnosis of *Streptococcus pneumoniae* infections in adults with bacteraemia and community-acquired pneumonia: clinical comparison of pneumococcal PCR and urinary antigen detection. *J Clin Microbiol* 2009; 47: 1046–1049.
66. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections – full version. *Clin Microbiol Infect* 2011; 17: Suppl. 6, E1–E59.
67. Frost PJ, Wise MP. Early management of acutely ill ward patients. *BMJ* 2012; 345: e5677.
68. Lim WS, van der Eerden MM, Laing R, *et al.* Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003; 58: 377–382.
69. Loke YK, Kwok CS, Niruban A, *et al.* Value of severity scales in predicting mortality from community-acquired pneumonia: systematic review and meta-analysis. *Thorax* 2010; 65: 884–890.
70. Bont J, Hak E, Hoes AW, *et al.* Predicting death in elderly patients with community-acquired pneumonia: a prospective validation study reevaluating the CRB-65 severity assessment tool. *Arch Intern Med* 2008; 168: 1465–1468.
71. Francis NA, Cals JW, Butler CC, *et al.* Severity assessment for lower respiratory tract infections: potential use and validity of the CRB-65 in primary care. *Prim Care Respir J* 2012; 21: 65–70.
72. Lim WS, Woodhead M. British Thoracic Society adult community acquired pneumonia audit 2009/10. *Thorax* 2011; 66: 548–549.
73. Labarere J, Stone RA, Scott Obrosky D, *et al.* Factors associated with the hospitalization of low-risk patients with community-acquired pneumonia in a cluster-randomized trial. *J Gen Intern Med* 2006; 21: 745–752.
74. Plüddemann A, Thompson M, Heneghan C, *et al.* Pulse oximetry in primary care: primary care diagnostic technology update. *Br J Gen Pract* 2011; 61: 358–359.
75. Bowton DL, Scuderi PE, Haponik EF. The incidence and effect on outcome of hypoxemia in hospitalized medical patients. *Am J Med* 1994; 97: 38–46.
76. Blot SI, Rodriguez A, Solé-Violán J, *et al.* Effects of delayed oxygenation assessment on time to antibiotic delivery and mortality in patients with severe community-acquired pneumonia. *Crit Care Med* 2007; 35: 2509–2514.
77. Bewick T, Greenwood S, Lim WS. What is the role of pulse oximetry in the assessment of patients with community-acquired pneumonia in primary care? *Prim Care Respir J* 2010; 19: 378–382.
78. Aliberti S, Cilloniz C, Chalmers JD, *et al.* Multidrug-resistant pathogens in hospitalised patients coming from the community with pneumonia: a European perspective. *Thorax* 2013; 68: 997–999.

79. Simpson SA, Wood F, Butler CC. General practitioners' perceptions of antimicrobial resistance: a qualitative study. *J Antimicrob Chemother* 2007; 59: 292–296.
80. Wood F, Phillips C, Brookes-Howell L, *et al.* Primary care clinicians' perceptions of antibiotic resistance: a multi-country qualitative interview study. *J Antimicrob Chemother* 2013; 68: 237–243.
81. Simpson SA, Wood F, Butler CC. General practitioners' perceptions of antimicrobial resistance: a qualitative study. *J Antimicrob Chemother* 2007; 59: 292–296.
82. Goossens H, Ferech M, Vander Stichele R, *et al.* Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; 365: 579–587.
83. Butler CC, Hood K, Verheij T, *et al.* Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. *BMJ* 2009; 338: b2242.
84. Brookes-Howell L, Hood K, Cooper L, *et al.* Clinical influences on antibiotic prescribing decisions for lower respiratory tract infection: a nine country qualitative study of variation in care. *BMJ Open* 2012; 2: e000795.
85. Brookes-Howell L, Hood K, Cooper L, *et al.* Understanding variation in primary medical care: a nine-country qualitative study of clinicians' accounts of the non-clinical factors that shape antibiotic prescribing decisions for lower respiratory tract infection. *BMJ Open* 2012; 2: e000796.
86. Wood J, Butler CC, Hood K, *et al.* Antibiotic prescribing for adults with acute cough/lower respiratory tract infection: congruence with guidelines. *Eur Respir J* 2011; 38: 112–118.
87. Coenen S, Francis N, Kelly M, *et al.* Are patient views about antibiotics related to clinician perceptions, management and outcome? A multi-country study in outpatients with acute cough. *PLoS One* 2013; 8: e76691.
88. Butler CC, Simpson SA, Dunstan F, *et al.* Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. *BMJ* 2012; 344: d8173.
89. Cals JW, Scheppers NA, Hopstaken RM, *et al.* Evidence based management of acute bronchitis; sustained competence of enhanced communication skills acquisition in general practice. *Patient Educ Couns* 2007; 68: 270–278.
90. Volpicelli G, Elbarbary M, Blaivas M, *et al.* International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med* 2012; 38: 577–591.
91. Shah VP, Tunik MG, Tsung JW. Prospective evaluation of point-of-care ultrasonography for the diagnosis of pneumonia in children and young adults. *JAMA Pediatr* 2013; 167: 119–125.
92. Reissig A, Copetti R, Mathis G, *et al.* Lung ultrasound in the diagnosis and follow-up of community-acquired pneumonia: a prospective, multicenter, diagnostic accuracy study. *Chest* 2012; 142: 965–972.
93. Caiulo VA, Gargani L, Caiulo S, *et al.* Lung ultrasound characteristics of community-acquired pneumonia in hospitalized children. *Pediatr Pulmonol* 2013; 48: 280–287.
94. Iuri D, De Candia A, Bazzocchi M. Evaluation of the lung in children with suspected pneumonia: usefulness of ultrasonography. *Radiol Med* 2009; 114: 321–330.
95. Cortellaro F, Colombo S, Coen D, *et al.* Lung ultrasound is an accurate diagnostic tool for the diagnosis of pneumonia in the emergency department. *Emerg Med J* 2012; 29: 19–23.
96. Parlamento S, Copetti R, Di Bartolomeo S. Evaluation of lung ultrasound for the diagnosis of pneumonia in the ED. *Am J Emerg Med* 2009; 27: 379–384.
97. Tsung JW, Kessler DO, Shah VP. Prospective application of clinician-performed lung ultrasonography during the 2009 H1N1 influenza A pandemic: distinguishing viral from bacterial pneumonia. *Crit Ultrasound J* 2012; 4: 16.
98. Testa A, Soldati G, Copetti R, *et al.* Early recognition of the 2009 pandemic influenza A (H1N1) pneumonia by chest ultrasound. *Crit Care* 2012; 16: R30.
99. Shyamsundar M, Attwood B, Keating L, *et al.* Clinical review: the role of ultrasound in estimating extra-vascular lung water. *Crit Care* 2013; 17: 237.
100. Li JZ, Winston LG, Moore DH, *et al.* Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. *Am J Med* 2007; 120: 783–790.
101. Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, *et al.* Short- *versus* long-course antibacterial therapy for community-acquired pneumonia: a meta-analysis. *Drugs* 2008; 68: 1841–1854.
102. Christ-Crain M, Stolz D, Bingisser R, *et al.* Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2006; 174: 84–93.
103. Long W, Deng X, Zhang Y, *et al.* Procalcitonin guidance for reduction of antibiotic use in low-risk outpatients with community-acquired pneumonia. *Respirology* 2011; 16: 819–824.
104. Wise MP, Howe RA, Butler CC. Containing antibiotic resistance while treating community-acquired pneumonia. *Arch Intern Med* 2011; 171: 1510.

Chapter 10

CAP in children

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SUMMARY: Community-acquired pneumonia (CAP) is one of the most common infections of infants and children in developing and industrialised countries. Given the clinical, social and economic importance of CAP for the paediatric age group, there is general agreement that a prompt and adequate therapeutic approach is essential in order to reduce the impact of the disease. However, there are various issues that make it difficult to establish a rational approach to the treatment of paediatric CAP, including difficulty in identifying the aetiology of the disease, the emergence of resistance of the most frequent bacterial pathogens to commonly used antibiotics, and the lack of certain information about the possible preventive role of the recently marketed pneumococcal vaccine. More research is required in many areas, including the aetiological agents associated with CAP complications, the absence of a paediatric CAP severity score, a better definition of second-line antibiotic therapies, how to follow-up on patients with CAP, and the cost-effectiveness of vaccines against respiratory pathogens.

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Community-acquired pneumonia (CAP) is one of the most frequent infections of infants and children in developing countries (where it is the commonest cause of paediatric death) and in industrialised countries, where it causes substantial morbidity-related socio-economic problems [1–3]. The definition of CAP is complex and varies widely in different guidelines: some are based on clinical judgement only, whereas others also take radiographic findings or laboratory data into account [4–6].

Given the clinical, social and economic importance of CAP, there is general agreement that a prompt and adequate therapeutic approach is essential in order to reduce the impact of the disease [4–6]. However, it is not easy to prescribe a rational and effective antimicrobial therapy, because it is very difficult to define the aetiology of CAP in paediatric patients, and because the recent emergence of resistance among the most common bacteria responsible for lower respiratory tract infections can make it difficult to eradicate them from the lung [6]. The aim of this chapter is to consider the available data concerning the management of paediatric CAP.

Aetiology

The aetiology of CAP is much more difficult to identify in children than in adults, because lower airway secretions can rarely be obtained and invasive diagnostic methods cannot routinely be used [2, 6–8]. In addition, as is the case in adults, cultures of upper respiratory tract secretions are not useful because normal flora frequently includes the bacteria commonly responsible for pneumonia [9].

The aetiological data of hospitalised children with CAP are similar to those of ambulatory children [6]. A number of studies have shown that respiratory viruses play the major role as single agents or co-pathogens with bacteria [10–12]. This is particularly evident during the first 2 years of life, when viruses can be demonstrated in about 80% of CAP cases [10–12]. The importance of viruses declines with age and only about one third of the CAP cases among subjects over 5 years of age are due to these infectious agents. The most frequently isolated viruses are rhinovirus, respiratory syncytial virus, influenza virus A and B, adenovirus and various enteroviruses. Bacteria can be demonstrated in about 30–40% of the cases in which an aetiological agent is identified [13–20]. Among children of all ages, *Streptococcus pneumoniae* seems to be the most important bacterial pathogen and accounts for about 30% of all cases [13–15]. After the introduction of heptavalent pneumococcal conjugate vaccine (PCV7) in Europe, real-time PCR and/or culture data indicated that serotypes 1 and 19A were the most common isolates in children with bacteraemic CAP. However, the majority of the other serotypes are included in 13-valent pneumococcal conjugate vaccine (PCV13) and, with the extended use of PCV13, paediatric pneumococcal CAP could be significantly reduced. *S. pneumoniae* is more important in children of pre-school age, because atypical bacteria (mainly *Mycoplasma pneumoniae*) seem to be the major aetiological agents in children over 5 years of age [16–18]. Up until a few years ago, it was believed that atypical bacteria did not play a significant role in CAP in younger children, but this has since been disproven. The importance of *Haemophilus influenzae* is declining regardless of age, particularly in areas in which conjugate vaccines are widely used, whereas *Staphylococcus aureus, Moraxella catarrhalis* and group A and B streptococci are rarely identified as bacterial causes of childhood CAP [19, 20]. Interestingly, recent studies showed that *Legionella pneumophila* is diagnosed more often in CAP than previously thought, accounting for up to 5% of paediatric CAP cases [21–23]. Table 1 summarises the most common bacteria identified in different age groups.

Virus and bacteria, or multi-bacterial co-infections, have been demonstrated in 16–34% of all childhood CAP cases [24]. The clinical implications of co-infections are still not clear, but the fact that they have been increasingly recognised over recent years demonstrates the complex aetiology of childhood CAP, which also means that identifying a potentially causative pathogen does not preclude the possibility of an aetiological contribution from others.

Despite the widely available data concerning the aetiology of CAP in infants and children, analysis of the methods used to perform relevant studies shows that reliable information can only be obtained if a number of sophisticated techniques are used simultaneously [2]. This may explain why only one third of childhood CAP cases are usually attributed to a specific aetiology.

Table 1. Principal bacteria causing childhood community-acquired pneumonia, by paediatric age group

Bacteria	Age group			
	Birth–1 month	1–3 months	4 months–4 years	5–18 years
Streptococcus pneumoniae	+	+++	++++	+++
Haemophilus influenzae	+	+	+	±
Streptococcus pyogenes	-	+	+	+
Staphylococcus aureus	++	++	+	+
Streptococcus agalactiae	+++	+	-	-
Escherichia coli	++	+	-	-
Mycoplasma pneumoniae	-	+	++	++++
Chlamydophyla pneumoniae	-	+	+	++
Legionella pneumophila	+	+	+	+
Chlamydia trachomatis	+	++	-	-
Bordetella pertussis	±	++	+	+

++++: very common; +++: common; ++: relatively uncommon; +: rare; ±: very rare; - absent. Adapted from PRINCIPI and ESPOSITO [2].

Moreover, the results of the many attempts to correlate epidemiological and clinical data, chest radiography findings and routine laboratory tests with the microbiological causes of CAP have been confusing. Studies of large series in which the investigators carefully verified the cause of paediatric CAP in relation to clinical or epidemiological findings have shown that signs and symptoms are surprisingly uniform throughout the aetiological spectrum [25, 26]. A number of studies flatly state that there are no differentiating radiological features [27, 28]. Non-microbiological laboratory tests, such as total and differential white blood cell counts, serum C-reactive protein levels and the erythrocyte sedimentation rate, may be affected by a number of physical, chemical or microbial stimuli, and are not much better than chest radiographs in the identification of aetiology. Previous studies have shown that C-reactive protein levels and absolute neutrophil counts were the most helpful, showing higher levels in pneumococcal CAP, although the dividing lines were not sharp [29–32]. The role of procalcitonin (PCT), a newly recognised marker of bacterial infection, has recently been studied for its ability to discriminate bacterial and viral aetiologies. Some studies found a threshold PCT concentration of 1 $g \cdot L^{-1}$ to be more sensitive and specific and show greater positive and negative predictive values than C-reactive protein or white blood cell count for differentiating bacterial and viral causes of CAP in untreated children admitted to hospital as emergency cases [33, 34].

All of these considerations mean that the signs and symptoms of CAP may be surprisingly uniform throughout the aetiological spectrum, that radiological characteristics cannot be used to distinguish different aetiological agents, and that non-microbiological laboratory tests are often not useful in individual cases.

Evaluating CAP severity

Children with CAP may present with fever, tachypnoea, breathlessness, difficulty breathing, cough, wheeze, headache, abdominal pain or chest pain and the severity of the condition can range from mild to life threatening (table 2) [4–6]. As CAP has a wide spectrum of presentations, and infants and children with mild or moderate respiratory symptoms can be safely managed in outpatient settings, evaluating severity is crucial. This also influences the need for microbiological investigations, initial antimicrobial therapy and the optimal level of medical care offered to each patient.

Infants and children with mild to moderate symptoms can be managed safely at home [4–6]. Those with signs of severe disease should be admitted to the hospital. Indicators for admission include hypoxaemia (arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) <90–93% and cyanosis), respiratory rate >70 $breaths \cdot min^{-1}$ in infants and >50 $breaths \cdot min^{-1}$ in older children,

Table 2. Severity assessment of community-acquired pneumonia, by paediatric age group

	Infants		Older children	
	Mild	**Severe**	**Mild**	**Severe**
Temperature °C	<38.5	38.5	<38.5	38.5
Respiratory rate breaths·min^{-1}	⩽70	>70	⩽50	>50
S_{pO_2} in room air %	⩾94	<90–93	⩾94	<90–93
Recession	Mild	Moderate to severe		
Breathing difficulty			Mild breathlessness	Severe difficulty
Other symptoms	Taking full meals	Nasal flaring, cyanosis, intermittent apnoea, grunting respiration, not eating	No vomiting	Nasal flaring, cyanosis, grunting respiration, signs of dehydration

S_{pO_2}: arterial oxygen saturation measured by pulse oximetry.

difficulty breathing, grunting, not eating or signs of dehydration, and inability of the family to provide appropriate observation or supervision [4–6]. However, the ultimate decision to admit a patient must be based on the overall clinical picture.

Hyponatraemia represents another important sign of severe CAP and the sodium ion concentration in the plasma should always be evaluated in children who require hospital admission [35]. Transfer to intensive care should be considered when the patient is failing to maintain an arterial oxygen saturation of >92% in inspiratory oxygen fraction of >0.6, the patient is shocked, there is a rising respiratory rate and rising pulse rate with clinical evidence of severe respiratory distress and exhaustion, and there is recurrent apnoea or slow irregular breathing [4–6]. A number of attempts have been made to correlate clinical findings with disease severity. However, unlike in adults, there is no validated clinical scoring system to predict which children have sufficiently severe CAP to warrant hospitalisation [2]. Hypoxaemia is usually considered the most reliable index of the need for hospitalisation but, although it is frequent in subjects with severe CAP, it may be absent in moderate cases. Moreover, experts do not agree on the cut-off level for identifying the cases that need hospitalisation. Most consider an S_{pO_2} measurement of <90% in room air at sea level in a previously healthy child to be a marker for immediate hospitalisation [5], but some prefer to consider oxygen saturation as high as 93%, if associated with a temperature of >39°C, tachycardia and a capillary refill time of >2 s [4–6].

Furthermore, although all of the experts consider young age another factor associated with more severe CAP, there is no general agreement concerning the age below which hospitalisation is necessary. Some suggest that infants aged up to 3 months should always be hospitalised, whereas others indicate an age of 6 months [4–6].

Diagnosis

One of the problems of paediatric CAP is its diagnosis. It is usually defined as the presence of signs and symptoms of lung disease in a previously healthy child, caused by an infection acquired outside a hospital [4–6]. The poor sensitivity of physical data in identifying mild or moderate CAP cases was clearly highlighted in recent studies of the association between historical and physical examination findings and radiographically confirmed CAP, which found that no physical test was perfectly sensitive in children [36, 37]. Furthermore, BILKIS *et al.* [38] found that the combination of fever, localised râles, decreased breathing sounds and tachypnoea was associated with radiographic pneumonia in only 69% of cases.

It used to be thought that the number of mistaken CAP diagnoses could be reduced by means of the systematic use of chest radiography in all children with suspected CAP. Unfortunately, this approach defines lung changes indicative of CAP in less than 20% of children with mild or moderate CAP [2]. Moreover, the interpretation of radiological findings in children with suspected CAP varies widely, even in well-trained reviewers, particularly in the presence of interstitial infiltrates [2]. Furthermore, unnecessary radiation exposure should be avoided because of the potential risk of malignancies [39]. This explains why all experts think that routine chest radiography is not essential to confirm suspected CAP in children who are well enough to be treated as outpatients, but should be strongly recommended for children with severe respiratory involvement, since the findings can not only confirm the diagnosis but also document the characteristics of the parenchymal infiltrates and the presence of complications requiring specific therapy. This means that diagnosing CAP in children with mild signs and symptoms remains a difficult problem, and that it is possible that a considerable number of patients without CAP (particularly those that are seen and treated in the community) may be treated in the same way as those with the disease (including unnecessary antibiotic administration).

Computed tomography (CT) is usually reserved for patients with CAP complicated by parapneumonic effusions, necrotising pneumonia or lung abscesses, especially when surgical

interventions are being considered [2]. Chest radiographs are less sensitive than CT scans in detecting lung abscesses, and fail in approximately 20% of cases [2]. Severe parapneumonic effusions and empyema (*i.e.* with more than half of the chest radiograph opacified) often require a CT scan before the placement of a chest tube, especially when loculated effusion is suspected [2]. In such cases, lung ultrasonography may be an alternative, as it has the advantage of bypassing radiation exposure, even though it is less accurate and gives rise to more inter-observer disagreement than a CT scan [5].

Antibiotic therapy

Theoretically, antibiotics should only be given to children with bacterial CAP. However, differentiating viral cases from bacterial is very difficult and frequently impossible in younger patients, even when microbiological methods are used to detect bacteria. Due to the risk of complications, lung puncture, bronchoalveolar lavage and thorascopic lung biopsy are reserved for complicated and life-threatening cases that do not respond to theoretically adequate antibiotic therapy [2, 4–6]. Blood cultures are positive in 13–26.5% of children with complicated CAP, but in less than 5% of those with mild or moderate disease [13–15]. Molecular methods can increase the sensitivity of identifying bacterial pathogens in blood samples, but they are not routinely used in all laboratories [13–15]. Gram staining and cultured expectorated sputum are widely used in adults to identify the bacteria responsible for CAP, but most children (particularly those in the first years of life) cannot provide adequate specimens for testing. Otherwise healthy younger children frequently carry nasopharyngeal bacteria that are the same as those that can cause CAP and so, when sputum is induced, contamination often leads to unreliable results [40]. Finally, the poor correlation between the bacteria carried and the bacteria involved in CAP means that the data coming from cultured nasopharyngeal secretions are not reliable for the diagnosis of bacterial CAP [40]. Urinary antigen tests have been found to be very effective in detecting *S. pneumoniae* in adults, but cannot be used to diagnose pneumococcal infection in the first years of life because positive findings do not reliably distinguish children with pneumococcal pneumonia from those who are merely colonised [41].

It is very difficult to identify atypical bacteria as a cause of CAP. Culturing respiratory secretions in order to identify *M. pneumoniae* is impractical in most laboratories, because it requires specific media and its slow growth means that it takes too long to obtain information useful for therapeutic decision-making. The presence of cold-reacting antibodies against red blood cells in serum was once considered a reliable index of *M. pneumoniae* infection, but the accuracy of this test has never been evaluated in children and so it is not currently recommended in paediatrics [42]. Serological methods (mainly enzyme assays) can detect specific IgM and IgG antibodies, and their sensitivity and specificity are good if two serum samples are evaluated (one collected in the acute phase and one during convalescence) [42]. However, once again, although useful for epidemiological studies, the findings cannot be used for making therapeutic decisions. Finally, although it is theoretically very sensitive and specific, PCR-based testing is not readily available or practical, and is not considered a standard means of identifying *M. pneumoniae* CAP [42]. The diagnostic tests used to identify *Chlamydophila pneumoniae* are even more limited because they are scarcely reliable and the performance of many of the serological assays is poor or inadequately validated [42].

Until recently, it was thought that identifying CAP-causing viruses in upper respiratory secretions was more reliable, because they were not thought to occur in healthy children. However, this assumption is now widely questioned, since healthy children have been shown to carry at least some of these viruses. Furthermore, viral/bacterial co-infections are common in many CAP cases and bacterial pathogens may play a more important role in conditioning clinical signs, symptoms and patient outcomes [43].

All of these considerations explain why the routine prescription of antibiotics when CAP is diagnosed is not always the proposed therapy [4–6]. Children (especially pre-schoolers who have

received conjugate pneumococcal vaccination) with mild CAP who can be closely followed up, and for whom all of the available epidemiological, clinical, laboratory and radiological data clearly suggest a viral infection, should be given symptomatic therapy alone [4–6]. However, a close follow-up should be ensured and re-evaluation considered, depending on the evolution of the disease. During the influenza season, the use of neuraminidase inhibitors can be considered in selected cases [5, 6].

There is a dearth of large-scale, pragmatic, randomised control trials of antibiotic choices for children with CAP. Empirical antibiotic treatment for paediatric CAP should be based on diagnostic algorithms that begin with the age of the patient and then consider local epidemiology, antimicrobial resistance rates and clinical factors (particularly disease severity), vaccination status, pharmacokinetic/pharmacodynamic characteristics, and finally the results of laboratory tests and chest radiography. Given the age-related importance of bacterial pathogens in determining CAP, affected children can be divided into four age groups (table 3).

During the first 4 weeks of life, the traditionally used combination of ampicillin (or amoxicillin) and aminoglycosides (mainly gentamicin) remains the treatment of choice, with a broad-spectrum parenteral cephalosporin as a potential alternative [6].

In patients aged 1–3 months, *S. pneumoniae* is the main bacterial cause of CAP, and a β-lactam antibiotic is the proposed first-line treatment [6]. *Chlamydia trachomatis* and *Bordetella pertussis* should be considered, especially in the presence of little or no fever and severe cough, and in such cases macrolides should be proposed [6].

In children aged between 4 months and 4 years, the main bacterial causative agent of CAP is still *S. pneumoniae*, but atypical bacteria (particularly *M. pneumoniae*) may play a significant role, especially in children aged >2 years. The proposed drugs are penicillin G or an aminopenicillin, of which the most widely used is amoxicillin. Clinical failures and children who are not fully immunised against *S. pneumoniae* and/or *H. influenzae* type b could be treated with amoxicillin/clavulanate or third-generation cephalosporins. Second-generation cephalosporins can be considered in areas with a low prevalence of *S. pneumoniae* penicillin resistance. In cases of severe CAP or suspected atypical bacteria, consideration can be given to combined therapy with a β-lactamase-resistant drug plus a macrolide [6].

The main cause of CAP in children and adolescents aged 5–18 years is *M. pneumoniae*, although *S. pneumoniae* still plays a significant aetiological role, particularly in more severe cases [6]. Macrolides are the first-line drugs in mild and moderate cases, whereas combined β-lactam and macrolide therapy can be considered in more severe cases [2].

In all age groups, an anti-staphylococcal antibiotic should be considered in critically ill patients [6]. As they are not approved for the regular treatment of children and can lead to the selection of resistant strains, quinolones should only be used in selected cases if there are no other effective alternatives (*e.g.* macrolide-resistant *M. pneumonia*e infections with persistent symptoms), or in children with IgE-mediated allergy to β-lactams [6].

There are no published studies supporting the superiority of intravenous treatment or indicating the best time to switch from parenteral to oral treatment. In cases initially treated with *i.v.* antibiotics, a switch to oral therapy should be encouraged as soon as the child's clinical condition has improved (*i.e.* a decrease in temperature) and oral drugs are tolerated [6].

Although the duration of antimicrobial therapy has not been defined on the basis of the findings of randomised controlled studies, the recommended duration of antimicrobial therapy is 7–10 days for mild/moderate CAP [2, 6]. However, a shorter duration of treatment for uncomplicated CAP appeared effective in some studies [44, 45] and the use of PCT resulted in a valid guidance for reducing the duration of antimicrobial treatment in other reports [34, 46], although further research is needed to confirm its efficacy. A longer treatment (*i.e.* ⩾14 days) should be used in cases of severe and/or complicated CAP.

Table 3. Suggested antibiotic treatments for community-acquired pneumonia, by paediatric age group

Age group	Recommended treatment	Alternative treatment
Birth–1 month[#]	Ampicillin *i.v.* and aminoglycoside *i.v.* (*i.e.* gentamicin) (dose depends on weight and gestational age)	Cefotaxime *i.v.* (dose depends on weight and gestational age); Erythromycin (40 mg·kg^{-1}·day^{-1} in 3–4 divided doses) oral or parenteral[¶]
1–3 months[#]	Oral amoxicillin or ampicillin *i.v.* (50–90 mg·kg^{-1}·day^{-1} in 2–3 doses) for 7–10 days; Erythromycin (40 mg·kg^{-1}·day^{-1} in 3–4 divided doses) or oral or parenteral clarithromycin (4–8 mg·kg^{-1}·day^{-1} *i.v.* in two divided doses or 15 mg·kg^{-1}·day^{-1} orally in two divided doses) for 10–14 days or oral azithromycin (10 mg·kg^{-1}·day^{-1} in one dose for 3 days or one dose of 10 mg·kg^{-1}·day^{-1} and then 5 mg·kg^{-1}·day^{-1} for 4 days)[#,¶]	Oral amoxicillin/clavulanate (amoxicillin component: 50–90 mg·kg^{-1}·day^{-1} in 2–3 doses) for 7–10 days (5–7 days may be adequate); Benzylpenicillin *i.v.* 200 000 units·kg^{-1}·day^{-1} in 4–6 doses; Ceftriaxone *i.v.* (50–100 mg·kg^{-1} once a day) or cefotaxime *i.v.* (100–150 mg·kg^{-1}·day^{-1} in three divided doses)
4 months–4 years	Oral amoxicillin or ampicillin *i.v.* (50–90 mg·kg^{-1}·day^{-1} in 2–3 doses) for 7–10 days (5–7 days may be adequate)	Oral amoxicillin/clavulanate (amoxicillin component: 50–90 mg·kg^{-1}·day^{-1} in 2–3 doses) for 7–10 days (5–7 days may be adequate); Oral cefuroxime axetil (30 mg·kg^{-1}·day^{-1} in two divided doses); Benzylpenicillin *i.v.* 200 000 units·kg^{-1}·day^{-1} in 4–6 doses; Ceftriaxone *i.v.* (50–100 mg·kg^{-1} once a day) or cefotaxime *i.v.* (100–150 mg·kg^{-1}·day^{-1} in three divided doses); Oral cephalexine or *i.v.* cloxacillin, cephazoline or vancomycin;[+] Erythromycin oral or parenteral (40 mg·kg^{-1}·day^{-1} in 3–4 divided doses), or oral or parenteral clarithromycin (4–8 mg·kg^{-1}·day^{-1} *i.v.* in two divided doses or 15 mg·kg^{-1}·day^{-1} orally in two divided doses) for 10–14 days, or oral azithromycin (10 mg·kg^{-1}·day^{-1} in one dose for 3 days or one dose of 10 mg·kg^{-1}·day^{-1} and then 5 mg·kg^{-1}·day^{-1} for 4 days)[¶]
5–18 years	Oral amoxicillin or ampicillin *i.v.* (50–90 mg·kg^{-1}·day^{-1} in 2–3 doses) for 7–10 days (5–7 days may be adequate); Erythromycin oral or parenteral (40 mg·kg^{-1}·day^{-1} in 3–4 divided doses), or oral or parenteral clarithromycin (4–8 mg·kg^{-1}·day^{-1} *i.v.* in two divided doses or 15 mg·kg^{-1}·day^{-1} orally in two divided doses) for 10–14 days, or oral azithromycin (10 mg·kg^{-1}·day^{-1} in one dose for 3 days or one dose of 10 mg·kg^{-1}·day^{-1} and then 5 mg·kg^{-1}·day^{-1} for 4 days)[¶]	Benzylpenicillin *i.v.* 200 000 units·kg^{-1}·day^{-1} in 4–6 doses; Ceftriaxone *i.v.* (50 mg·kg^{-1} once a day) or cefotaxime *i.v.* (100–150 mg·kg^{-1}·day^{-1} in three divided doses); Oral cephalexine or *i.v.* cloxacillin, cephazoline or vancomycin[+]

[#]: in infants aged <6 weeks, treatment with clarithromycin or azithromycin should be recommended because there have been reports of hypertrophic pyloric stenosis as well as torsade de pointes in infants receiving erythromycin; [¶]: in cases of *Mycoplasma pneumoniae, Chlamydia trachomatis, Chlamydophila pneumoniae* or *Bordetella pertussis*; [+]: staphylococcal pneumonia is unusual; however, if cultures of blood or pleural fluid grow *Staphylococcus aureus*, oxacillin or (in areas where methicillin-resistant *S. aureus* is a reasonable possibility) vancomycin should be added.

Conclusions

There are various reasons that make it difficult to establish a rational approach to the treatment of CAP in infants and children, including the difficulty of identifying the aetiology of the disease, the emergence of resistance of the most frequent bacterial pathogens to commonly used antibiotics, and the lack of certain information about the possible preventive role of the recently marketed pneumococcal vaccine. Therefore, paediatricians tend to use antibiotics to treat almost all cases of CAP, including those that are more likely due to viruses but cannot be immediately identified as such. Furthermore, the fact that it is usually impossible to differentiate infections due to typical or atypical bacteria in individual patients means that paediatricians typically tend to prescribe an antibiotic combination for all children older than 4 months, in order to cover all of the possible infectious agents.

More research is clearly required in various areas, such as the aetiological agents associated with CAP complications, the absence of a paediatric CAP severity score, a better definition of second-line antibiotic therapies, and how to follow-up on patients with CAP. Further efforts are needed to increase vaccination coverage with the already available vaccines against respiratory pathogens and to conduct prospective studies of their impact, including an evaluation of their cost-effectiveness.

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References

1. Esposito S, Principi N. Unsolved problems in the approach to pediatric community-acquired pneumonia. *Curr Opin Infect Dis* 2012; 25: 286–291.
2. Principi N, Esposito S. Management of severe community-acquired pneumonia of children in developing and developed countries. *Thorax* 2011; 66: 815–822.
3. Cardinale F, Cappiello AR, Mastrototaro MF, *et al.* Community-acquired pneumonia in children. *Early Hum Dev* 2013; 89: Suppl. 3, S49–S52.
4. Harris M, Clark J, Coote N, *et al.* British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. *Thorax* 2011; 66: Suppl. 2, ii1–ii23.
5. Bradley JS, Byington CL, Shah SS, *et al.* Executive summary: the management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2011; 53: 617–630.
6. Esposito S, Cohen R, Domingo JD, *et al.* Antibiotic therapy for pediatric community-acquired pneumonia: do we know when, what and for how long to treat? *Pediatr Infect Dis J* 2012; 31: e78–e85.
7. McCracken GH Jr. Etiology and treatment of pneumonia. *Pediatr Infect Dis J* 2000; 19: 373–377.
8. McIntosh K. Community-acquired pneumonia in children. *N Engl J Med* 2002; 346: 429–437.
9. Menéndez R, Córdoba J, de la Cuadra P, *et al.* Value of the polymerase chain reaction assay in noninvasive respiratory samples for diagnosis of community-acquired pneumonia. *Am J Respir Crit Care Med* 1999; 159: 1868–1873.
10. Ruuskanen O, Lahti E, Jennings LC, *et al.* Viral pneumonia. *Lancet* 2011; 377: 1264–1275.
11. Pavia AT. Viral infections of the lower respiratory tract: old viruses, new viruses, and the role of diagnosis. *Clin Infect Dis* 2011; 52: Suppl. 4, S284–S289.
12. Esposito S, Daleno C, Prunotto G, *et al.* Impact of viral infections in children with community-acquired pneumonia: results of a study of 17 respiratory viruses. *Influenza Other Respir Viruses* 2013; 7: 18–26.
13. Resti M, Moriondo M, Cortimiglia M, *et al.* Community-acquired bacteremic pneumococcal pneumonia in children: diagnosis and serotyping by real-time polymerase chain reaction using blood samples. *Clin Infect Dis* 2010; 51: 1042–1049.
14. Esposito S, Marchese A, Tozzi AE, *et al.* DNA bacterial load in children with bacteremic pneumococcal community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis* 2013; 32: 877–881.

15. Esposito S, Marchese A, Tozzi AE, *et al.* Bacteremic pneumococcal community-acquired pneumonia in children less than 5 years of age in Italy. *Pediatr Infect Dis J* 2012; 31: 705–710.
16. Esposito S, Bosis S, Cavagna R, *et al.* Characteristics of *Streptococcus pneumoniae* and atypical bacterial infections in children 2–5 years of age with community-acquired pneumonia. *Clin Infect Dis* 2002; 35: 1345–1352.
17. Cardinale F, Chironna M, Dumke R, *et al.* Macrolide-resistant *Mycoplasma pneumoniae* in paediatric pneumonia. *Eur Respir J* 2011; 37: 1522–1524.
18. Cardinale F, Chironna M, Chinellato I, *et al.* Clinical relevance of *Mycoplasma pneumoniae* macrolide resistance in children. *J Clin Microbiol* 2013; 51: 723–724.
19. Murphy TF, Faden H, Bakaletz LO, *et al.* Nontypeable *Haemophilus influenzae* as a pathogen in children. *Pediatr Infect Dis J* 2009; 28: 43–48.
20. Otter JA, French GL. Molecular epidemiology of community-associated meticillin-resistant *Staphylococcus aureus* in Europe. *Lancet Infect Dis* 2010; 10: 227–239.
21. Graham FF, White PS, Harte DJ, *et al.* Changing epidemiological trends of legionellosis in New Zealand, 1979–2009. *Epidemiol Infect* 2012; 140: 1481–1496.
22. Heine S, Fuchs A, von Müller L, *et al.* Legionellosis must be kept in mind in case of pneumonia with lung abscesses in children receiving therapeutic steroids. *Infection* 2011; 39: 481–484.
23. Klapdor B, Ewig S, Pletz MW, *et al.* Community-acquired pneumonia in younger patients is an entity on its own. *Eur Respir J* 2012; 39: 1156–1161.
24. Heiskanen-Kosma T, Korppi M, Jokinen C, *et al.* Etiology of childhood pneumonia: serologic results of a prospective, population-based study. *Pediatr Infect Dis J* 1998; 17: 986–991.
25. Turner RB, Lande AE, Chase P, *et al.* Pneumonia in pediatric outpatients: cause and clinical manifestations. *J Pediatr* 1987; 111: 194–200.
26. Principi N, Esposito S, Blasi F, *et al.* Role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in children with community-acquired lower respiratory tract infections. *Clin Infect Dis* 2001; 32: 1281–1289.
27. Courtoy I, Lande AE, Turner RB. Accuracy of radiographic differentiation of bacterial from nonbacterial pneumonia. *Clin Pediatr* 1989; 28: 261–264.
28. Korppi M, Kiekara O, Heiskanen-Kosma T, *et al.* Comparison of radiological findings and microbial aetiology of childhood pneumonia. *Acta Paediatr* 1993; 82: 360–363.
29. Nohynek H, Valkeila E, Leinonen M, *et al.* Erythrocyte sedimentation rate, white blood cell count and serum C-reactive protein in assessing etiologic diagnosis of acute lower respiratory infections in children. *Pediatr Infect Dis J* 1995; 14: 484–490.
30. Korppi M, Heiskanen-Kosma T, Leinonen M. White blood cells, C-reactive protein and erythrocyte sedimentation rate in pneumococcal pneumonia in children. *Eur Respir J* 1997; 10: 1125–1129.
31. Galetto-Lacour A, Alcoba G, Posfay-Barbe KM, *et al.* Elevated inflammatory markers combined with positive pneumococcal urinary antigen are a good predictor of pneumococcal community-acquired pneumonia in children. *Pediatr Infect Dis J* 2013; 32: 1175–1179.
32. Porfyridis I, Georgiadis G, Vogazianos P, *et al.* CRP, PCT, CPIS and pneumonia severity scores in nursing home acquired pneumonia. *Respir Care* 2013 [In press DOI: 10.4187/respcare.02741].
33. Korppi M, Remes S. Serum procalcitonin in pneumococcal pneumonia in children. *Eur Respir J* 2001; 17: 623–627.
34. Esposito S, Tagliabue C, Picciolli I, *et al.* Procalcitonin measurements for guiding antibiotic treatment in pediatric pneumonia. *Respir Med* 2011; 105: 1939–1945.
35. Wrotek A, Jackowska T. Hyponatremia in children hospitalized due to pneumonia. *Adv Exp Med Biol* 2013; 788: 103–108.
36. Neuman MI, Monuteaux MC, Scully KJ, *et al.* Prediction of pneumonia in a pediatric emergency department. *Pediatrics* 2011; 128: 246–253.
37. Patria MF, Longhi B, Lelii M, *et al.* Association between radiological findings and severity of community-acquired pneumonia in children. *Ital J Pediatr* 2013; 39: 56.
38. Bilkis MD, Gorgal N, Carbone M, *et al.* Validation and development of a clinical prediction rule in clinically suspected community-acquired pneumonia. *Pediatr Emerg Care* 2010; 26: 399–405.
39. Neuman MI, Lee EY, Bixby S, *et al.* Variability of the interpretation of chest radiographs for the diagnosis of pneumonia in children. *J Hosp Med* 2012; 7: 294–298.
40. De Schutter I, De Wachter E, Crokaert F, *et al.* Microbiology of bronchoalveolar lavage fluid in children with acute nonresponding or recurrent community-acquired pneumonia: identification of nontypeable *Haemophilus influenzae* as a major pathogen. *Clin Infect Dis* 2011; 52: 1437–1444.
41. Esposito S, Bosis S, Colombo R, *et al.* Evaluation of rapid assay for detection of *Streptococcus pneumoniae* urinary antigen among infants and young children with possible invasive pneumococcal disease. *Pediatr Infect Dis J* 2004; 23: 365–367.
42. Principi N, Esposito S. Emerging role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in paediatric respiratory-tract infections. *Lancet Infect Dis* 2001; 1: 334–344.
43. Jansen RR, Wieringa J, Koekkoek SM, *et al.* Frequent detection of respiratory viruses without symptoms: toward defining clinically relevant cutoff values. *J Clin Microbiol* 2011; 49: 2631–2636.

44. Atkinson M, Lakhanpaul M, Smyth A, *et al.* Comparison of oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia in children (PIVOT trial): a multicentre pragmatic randomised controlled equivalence trial. *Thorax* 2007; 62: 1102–1106.
45. Peltola H, Vuori-Holopainen E, Kallio MJ, *et al.* Successful shortening from seven to four days of parenteral β-lactam treatment for common childhood infections: a prospective and randomized study. *Int J Infect Dis* 2001; 5: 3–8.
46. Baer G, Baumann P, Buettcher M, *et al.* Procalcitonin guidance to reduce antibiotic treatment of lower respiratory tract infection in children and adolescents (ProPAED): a randomized controlled trial. *PLoS One* 2013; 8: e68419.

Chapter 11

Empirical antibiotic management of adult CAP

Mark Woodhead and Muhammad Noor

SUMMARY: In adults who present with community-acquired pneumonia, it has become standard practice to commence empirical antibiotic therapy without waiting for the results of tests to identify the microbial cause. The reasons for this include the morbidity and mortality of the condition and the lack of sensitivity of microbial tests. In addition to reviewing the evidence behind these statements, this chapter describes the available antibiotics, and the international guideline recommendations for empirical antibiotic therapy and the reasons for the recommendations.

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Community-acquired pneumonia (CAP) remains a serious infectious disease even in the modern era of antibiotics with mortality rates between 8% and 15% in hospitalised patients [1–3]. The mortality from CAP has not improved significantly since antimicrobial agents were first introduced in the 1940s [4]. Because of the large number of organisms that may cause CAP, the inexactness of commonly used diagnostic techniques and the serious consequences of untreated disease, empirical therapy has become an accepted practice. Recent evidence suggests the superiority of combination therapy compared with monotherapy in patients with severe CAP [5–19]. Empirical therapy should be designed for treatment of the most likely causative organisms while minimising the potential adverse effects of therapy, drug toxicity and excessive cost. It should be based on local, national or international CAP guideline recommendations, but may be modified in the individual patient by factors such as penicillin allergy, the need for oral or parenteral therapy, concomitant medications, illness severity, local bacterial resistance patterns and place of care.

Rationale for empirical therapy

There are three main reasons for favouring empirical antibiotic therapy: 1) the causative pathogen cannot usually be predicted from presenting clinical, laboratory and radiographic features; 2) microbiological tests are insensitive and, at best, provide information hours or days after patient presentation; and 3) delay in appropriate antibiotic therapy may be associated with significant mortality.

As each new bacterial cause of pneumonia was identified through the late 19th and 20th century, they were initially linked with a unique clinical presentation, only for this illusion to be shattered. The explanation is that new causes are, in general, initially found only in extreme cases and then,

as the search widens, other previously missed cases are found. The link between the so-called atypical pneumonia syndrome and infection with *Mycoplasma pneumoniae* is the most important example, but the same has been seen with *Legionella* infection. In reality, it appears that all organisms cause a spectrum of clinical and laboratory presentation. While extreme cases may be recognisable, when critically compared, there is too much overlap in clinical and laboratory features to make such pathogen recognition useful in routine clinical practice [20]. The same is true of chest radiography. The chest radiograph is a very useful test to establish the diagnosis of CAP, but it is unlikely to confirm the pathogen involved. Cavitation is about the only useful finding as this may be a predictor of staphylococcal, anaerobic or Gram-negative bacterial infection.

Microbial investigation

Blood cultures are positive in <5% of cases [21], and rarely alter empirical antibiotic therapy and, even when there is a change, it mostly does not improve patient outcome [22].

Sputum is the other commonly used sample in microbial investigation in CAP. A sputum specimen may not be available in up to one-third of patients with CAP. Indeed, recent data show that an adequate specimen with a predominant morphotype on Gram staining was found in only 14% of 1669 hospitalised patients with CAP [23], and its use was without noticeable benefit in the clinical management of CAP inpatients [24].

The newest tests for microbial aetiology of CAP are the urinary antigen tests. Two recent studies showed no significant benefit in patient management [25, 26]. Prior antibiotic therapy is another factor limiting the usefulness of conventional bacteriology [27].

The latest advance in microbiological diagnosis has been the introduction of molecular tests to detect pathogen-specific RNA or DNA. The cost effectiveness of such tests has yet to be evaluated in CAP management, but it is unlikely that they will remove the need for empirical therapy. As indicated in previous studies [27, 28], even when a combination of microbial tests is undertaken, the aetiological yield is low in routine clinical practice.

Despite this, microbiology and microbiological investigation is still relevant in CAP and is discussed in more detail in the chapter by LUNG and RELLO [29].

Need for early antibiotic therapy

Although early administration of appropriate antimicrobial treatment has not been directly correlated with better prognosis [30–39], there have been a number of studies that suggest that delay and inadequate therapy for infections in critically ill patients is associated with poor outcomes, including greater morbidity and mortality, and increased length of stay [40–42]. In a large retrospective study of 13 771 Medicare patients, antibiotic administration within 4 h of hospital arrival was associated with significant reduction in mortality (6.8% compared with 7.4%) and length of stay (0.4 days shorter) [43]. Similar results were obtained in other studies [44–46] but others have found no influence of antibiotic timing on outcome [47]. Therefore, the timing of initial therapy should be guided by the urgency of the situation. In critically ill patients, such as those in septic shock and patients with other significant comorbid medical problems, empirical therapy should be initiated within 1 h [48]. In other, more stable clinical circumstances, early antibiotic administration has been associated with a lower mortality [49, 50] and should be normal practice.

Choice of empirical antibiotics

There are a number of antibiotics available that could be chosen, individually or in combination, to treat one or more of the known microbial causes of CAP [29].

Penicillins

Penicillins have been the most widely used antibiotics over the past 50 years. They are inexpensive and widely available, and are often the first-line treatment of choice for CAP. They contain a β-lactam ring and prevent cell wall synthesis by binding to penicillin-binding proteins (PBPs). β-lactam antibiotics inhibit the formation of peptidoglycan cross-links in the bacterial cell wall, which is achieved through binding of the four-membered β-lactam ring of penicillin to the enzyme D,D-transpeptidase. Consequently, D,D-transpeptidase cannot catalyse formation of these cross-links and an imbalance between cell wall production and degradation develops, causing the cell to die rapidly. This is of particular importance for *Streptococcus pneumoniae*, where the cell wall is composed of peptidoglycan containing PBPs with particular affinity for penicillin. In the management of CAP, the main weakness of the penicillins is their ineffectiveness against the so-called atypical pathogens, *M. pneumoniae*, *Chlamydophila*, *Coxiella* and *Legionella*.

Common adverse reactions associated with use of the penicillin include diarrhoea, hypersensitivity, nausea, rash, neurotoxicity, urticaria and candidiasis. Infrequent adverse effects include fever, vomiting, erythema, dermatitis, angio-oedema, seizures and *Clostridium difficile* infection including pseudomembranous colitis.

Penicillins are further sub-classified based on chemical structure (*e.g.* penicillins, monobactams and carbapenems), spectrum (narrow, broad or extended) source (natural, semisynthetic or synthetic) and susceptibility to β-lactamase destruction.

Narrow-spectrum β-lactamase-sensitive penicillins

This group includes naturally occurring penicillin G (benzylpenicillin) in its various pharmaceutical forms and a few biosynthetic forms. Penicillins in this class are active against many Gram-positive and a limited number of Gram-negative bacteria, as well as anaerobic organisms, but they are susceptible to hydrolysis by β-lactamase (penicillinase). While very effective *via* parenteral administration, absorption of oral preparations may be unreliable.

Narrow-spectrum β-lactamase-resistant penicillins

This group is refractory to a greater or lesser degree to the effects of various β-lactamase enzymes produced by resistant Gram-positive organisms, particularly *Staphylococcus aureus*. However, penicillins in this class are not as active against many Gram-positive bacteria as penicillin G and are inactive against almost all Gram-negative bacteria. Members of this group include isoxazolylpenicillins, such as oxacillin, cloxacillin, dicloxacillin and flucloxacillin.

Broad-spectrum β-lactamase-sensitive penicillins

Penicillins in this class are active against many Gram-positive and Gram-negative bacteria. However, they are readily destroyed by the β-lactamases (produced by many bacteria). Of those used in medicine, aminopenicillins (*e.g.* ampicillin and amoxicillin) are the best known and are valued because of their excellent oral bioavailability. Several semisynthetic, broad-spectrum penicillins are also active against *Pseudomonas aeruginosa*, including certain *Proteus* spp. and, in certain cases, strains of *Klebsiella*, *Shigella* and *Enterobacter* spp. Examples of this class include carboxypenicillins (carbenicillin and ticarcillin), ureido-penicillins (azlocillin and mezlocillin), and piperazine penicillins (piperacillin).

β-lactamase-protected broad-spectrum penicillins

Several naturally occurring and semisynthetic compounds can inhibit many of the β-lactamase enzymes produced by penicillin-resistant bacteria. When used in combination with broad-spectrum penicillins, there is a notable synergistic effect because the active penicillin is protected

from enzymatic hydrolysis and thus is fully active against a wide variety of previously resistant bacteria. Examples of this chemotherapeutic approach include clavulanate-potentiated amoxicillin and ticarcillin, as well as sulbactam-potentiated ampicillin and tazobactam-potentiated piperacillin. Clavulanate potentiated amoxicillin is of particular use in the treatment of *Haemophilus influenzae* but hepatotoxicity is a harmful side-effect occurring in approximately one per 10 000 prescriptions [51].

Carbapenems

Carbapenems (imipenem and meropenem) are a class of β-lactam antibiotics that are among the most broadly active antibiotics available for systemic use in humans. They are active against *Streptococcus*, methicillin-sensitive *S. aureus*, *Neisseria*, *Haemophilus*, anaerobes and common aerobic Gram-negative nosocomial pathogens including *Pseudomonas*.

Macrolides

The antimicrobial spectrum of macrolides is wider than that of penicillins, therefore, macrolides are a common substitute for patients with a penicillin allergy. Unlike penicillins, macrolides have been shown to be effective against *Legionella*, *Mycoplasma*, *Chlamydophila* and *Coxiella*.

Macrolides are protein synthesis inhibitors. Four modes of protein synthesis inhibition have been ascribed to macrolides: 1) inhibition of the progression of the nascent peptide chain during early rounds of translation [52, 53]; 2) promotion of peptidyl transfer RNA (tRNA) dissociation from the ribosome [54]; 3) inhibition of peptide bond formation [52]; and 4) interference with 50S subunit assembly [55]. All of these mechanisms have some correlation with the location of the macrolide binding site on the ribosome. Macrolide maintenance therapy has been proven to be of benefit in diffuse panbronchiolitis and cystic fibrosis, presumably due to an anti-inflammatory mechanism of action in addition to its direct antimicrobial effect. The role of this anti-inflammatory effect in CAP is unknown and is discussed in more detail in the chapter by SALIH *et al.* [56].

Side-effects of using macrolides are experienced by 5–10% of all people. The most common side-effect is a gastrointestinal disturbance (more common with erythromycin) that can manifest itself as nausea, abdominal discomfort or diarrhoea. In addition to these side-effects, macrolides can cause headache and changes in taste. Macrolide use can cause pseudomembranous colitis. Other serious adverse effects include fever, confusion, bloody diarrhoea, hallucinations and depression or sudden mood swings. Development of macrolide resistance among respiratory pathogens is common during long-term macrolide treatment. Macrolides also prolong the QT interval and have been associated with sudden cardiac death. Interaction with other drugs (*e.g.* theophyllines) is an important limitation to their use in some patients.

Several macrolide agents are available for the treatment of CAP and among them, clarithromycin, erythromycin, azithromycin or roxithromycin are the most commonly used. Studies suggest azithromycin offers the potential advantages of short-course administration and lower toxicity compared to other macrolides for the treatment of mild pneumonia, but may be more likely to generate bacterial resistance [57].

Telithromycin is the first of the ketolide antibiotics to enter clinical use and is derived from the macrolide family. It is active against *S. pneumoniae* that is resistant to other antimicrobials commonly used for CAP (including penicillin, macrolides and fluoroquinolones). Several CAP trials suggest that telithromycin is equivalent to comparators (including amoxicillin, clarithromycin and trovafloxacin) [58–61]; however, hepatotoxicity has limited its generalised use [62].

Tetracyclines

Tetracyclines are characterised by their exceptional chemotherapeutic efficacy against a wide range of Gram-positive and Gram-negative bacteria. The tetracycline molecule comprises a linear-fused

tetracyclic nucleus to which a variety of functional groups are attached. The simplest tetracycline to display detectable antibacterial activity is 6-deoxy-6-demethyltetracycline and so this structure may be regarded as the minimum pharmacophore.

Tetracycline works by binding specifically to the 30S ribosome of bacteria, preventing attachment of the aminoacyl-tRNA to the RNA–ribosome complex. It simultaneously inhibits other steps of protein biosynthesis. Tetracycline can also alter the cytoplasmic membrane and this, in turn, causes leakage of nucleotides and other compounds out of the cell. Doxycycline is one of the most active tetracyclines and is the one most often used clinically since it possesses advantages over traditional tetracycline and minocycline, especially for once daily dosing.

Common side-effects include staining of developing and permanent teeth (thus contraindicated in females of childbearing age and children), skin photosensitivity, hepatitis and drug-induced lupus.

Quinolones

Quinolones belong to a group of synthetic antibiotics that are derived from the basic structure of nalidixic acid and have a ketone at position 4 and carboxylic group at position 3. Quinolones rapidly inhibit DNA synthesis by promoting cleavage of bacterial DNA in the DNA–enzyme complexes of DNA gyrase and type IV topoisomerase, resulting in rapid bacterial death. Quinolones can be classified into four generations based on antimicrobial activity (table 1). First-generation quinolones, which are used less often today, have moderate Gram-negative activity and minimal systemic distribution. Second generation quinolones have expanded Gram-negative activity and atypical pathogen coverage, but their main limitation is limited Gram-positive activity, especially against *S. pneumoniae*. These agents are most active against aerobic Gram-negative bacilli. Ciprofloxacin remains the quinolone most active against *P. aeruginosa*. Third generation quinolones retain expanded Gram-negative and atypical intracellular activity but have improved Gram-positive coverage. Finally, fourth-generation quinolones improve Gram-positive coverage, maintain Gram-negative coverage and gain anaerobic coverage.

Older fluoroquinolones lack activity against *S. pneumoniae*, limiting their value in CAP. Third- and fourth-generation fluoroquinolones are active against *S. pneumoniae* and are the first agents that are effectively active against all common CAP causes, hence their alternative name of respiratory fluoroquinolones.

Fluoroquinolones have broad-spectrum antimicrobial activity against pulmonary pathogens and are, therefore, recommended as first-line therapy for the treatment of CAP in adults [63, 64]. Older quinolones, such as ciprofloxacin, may be useful agents in the treatment of serious bronchopulmonary infections due to susceptible Gram-negative microorganisms such as *H. influenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae* and even *P. aeruginosa* [65–75]. A study of prescriptions written for outpatient treatment of CAP in the USA from November 2000 to January 2001 found that, of the nearly 1 million prescriptions for the five antibiotics routinely

Table 1. Classification of quinolones with antimicrobial spectrum

Generations	Quinolone	Microbiological activity
First	Nalidixic acid and cinoxacin	*Enterobacteriaceae*
Second	Class I: lomefloxacin, norfloxacin and enoxacin Class II: ofloxacin and ciprofloxacin	*Enterobacteriaceae*, atypical pathogens and *Pseudomonas aeruginosa* (ciprofloxacin only)
Third	Levofloxacin, sparfloxacin, gatifloxacin and moxifloxacin	*Enterobacteriaceae*, atypical pathogens, *Streptococcus*
Fourth	Trovafloxacin	*Enterobacteriaceae*, *Pseudomonas aeruginosa* (reduced or absent), atypical pathogens, methicillin-susceptible *Staphylococcus aureus*, *Streptococcus* and anaerobes

used for this indication (*i.e.* amoxicillin-clavulanic acid, azithromycin, clarithromycin, gatifloxacin and levofloxacin), fluoroquinolones accounted for 43% [76].

Concerns about the potential for rapid spread of bacterial resistance with widespread fluoroquinolone use have not been realised; however, they have been associated with a significant risk of *C. difficile* infection, thus limiting their widespread use, particularly in Europe. Another adverse event unique to the quinolones is tendinopathy. The European Medicines Agency has limited the use of oral moxifloxacin. Although it was stated that "the benefits continue to outweigh its risks", it was highlighted that it should only be prescribed in CAP when other antibiotics cannot be used or have failed. This recommendation was made mainly in view of an increased risk of adverse hepatic reactions. There is no evidence from the literature that moxifloxacin should be considered differently to levofloxacin in this regard. Moreover, there is evidence that liver toxicity is higher in amoxicillin-clavulanic acid than in respiratory quinolones [77].

Respiratory quinolones are now established treatment options [65–75]. However, the potentially small superiority of respiratory quinolones compared with penicillin and macrolides must be balanced against concerns of selection pressure, adverse events and cost [70].

Other agents

Two additional agents have been investigated in patients with CAP; tigecycline [66, 78] and ertapenem [79–81]. Ertapenem seems to be an attractive choice in patients at risk of Gram-negative enteric bacilli (GNEB) infection, particularly with extended-spectrum β-lactamases producing strains, but not in those at risk of *P. aeruginosa* infection [80–83]. Regular coverage of atypical pathogens may not be necessary in nonsevere hospitalised patients [84–87].

Route of administration

Good quality evidence to guide the route of initial therapy is lacking. It seems sensible for the parenteral route to be chosen for patients with altered consciousness and features that might suggest poor absorption of oral therapy, *e.g.* vomiting or diarrhoea. The parenteral route is usually recommended for more severely ill patients, while oral therapy is adequate for those who are less severely ill. Where the parenteral route is chosen, an early switch, guided by clinical response, to oral antibiotics is recommended. For certain antibiotics (*e.g.* carbapenems) only the parenteral route is available.

Single or dual antibiotics

Empirical therapy should be designed for treatment of the most likely causative organisms while minimising the potential adverse effects of therapy, drug toxicity and excessive cost. If a single organism caused CAP this would be easy, but we know that multiple organisms can cause CAP, a finding confirmed by recent studies [88, 89]. A recent analysis in Spain of 700 patients with CAP including 276 hospitalised and 424 ambulatory patients was able to define the aetiology of pneumonia in 55.7% (390 out of 700) of patients. The most frequently isolated organism was *S. pneumoniae* (170 (43.6%) out of 390 patients), followed by *Coxiella burnetii* (72 (18.5%) out of 390 patients), *M. pneumoniae* (62 (15.9%) out of 390), viruses as a group (56 (14.4%) out of 390 patients), *Chlamydia* spp. (39 (10.6%) out of 390 patients), and *Legionella pneumophila* (17 (4.4%) out of 390) [89]. A reduced frequency of CAP due to atypical organisms in more severely ill patients is found in most studies [88], where *S. pneumoniae*, *S. aureus* and *Legionella*, and in some studies GNEB, are most frequent. This is demonstrated by studies investigating the microbial cause of CAP according to site of care in the UK (fig. 1). In addition, it is believed that many infections caused by atypical organisms are self-limiting and poorly influenced by antibiotic therapy. For these reasons, in the nonseverely ill, antibiotic therapy does not need to cover *S. aureus*, *Legionella* or Gram-negative organisms. The need to cover *M. pneumoniae* is still under debate.

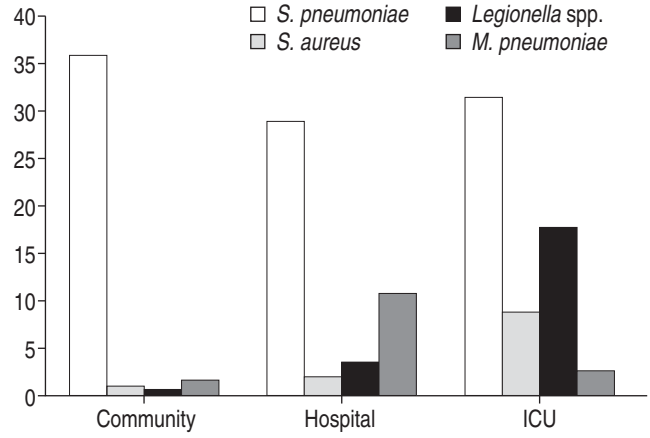

Figure 1. Aetiology of community-acquired pneumonia according to severity/site of management in the UK [90–97]. ICU: intensive care unit; *S. pneumoniae*; Streptococcus pneumonia; *S. aureus*; *Staphylococcus aureus*; *M. pneumoniae: Mycoplasma pneumoniae.*

Older studies from the USA suggest atypical organisms to be most important in mild illness, but European studies generally find *S. pneumoniae* to be the most common pathogen. Studies of outcome with antibiotics active against atypical organisms *versus* those not active against such organisms in nonsevere CAP have found similar success rates [98].

Several publications have demonstrated that low-level pneumococcal resistance to penicillin is not associated with adverse outcomes in the treatment of patients with CAP; therefore, penicillin is often the first-line drug in empirical treatment. In contrast with this, resistance to macrolides may result in clinical failure of response to macrolide treatment in patients with moderate-to-severe pneumonia [99, 100].

The other issue to consider is the risk of inappropriate antibiotic prescription. In the nonseverely ill patients this is small and there is usually time to change the antibiotic. However, in the more severely ill patient, it is vital to get the initial antibiotic prescription correct as there may be no time to change before the patient's clinical situation deteriorates.

From these two issues, the spectrum of microbial cause and the risk of inappropriate antibiotic prescription, both of which are related to illness severity, a general approach to empirical antibiotic prescription has arisen, with a narrow-spectrum antibiotic for nonsevere illness and a broad-spectrum antibiotic for the severely ill. This usually means a single antibiotic for the nonseverely ill and the combination of a β-lactam plus a macrolide, sometimes referred to as dual therapy, for the severely ill. An additional supporting, but currently unquantified, issue is the potential advantage of the additional anti-inflammatory effect of macrolides, but is there any evidence from antibiotic trials to indicate benefit from the dual approach in severe CAP?

Practice: what the studies show

A number of studies suggest the superiority of combination therapy compared with monotherapy, particularly in patients with severe CAP [5–19, 101] (table 2), as judged using mortality as the end-point. However, these studies share a common flaw. They are all retrospective and, therefore, potentially biased by intention to treat. In other words, the apparently better outcome with dual therapy may be related to a less severe case mix in those prescribed these antibiotics compared to those receiving monotherapy. This issue was highlighted in a similar study using propensity scores [102]. The most recent retrospective study found benefit from dual therapy in those with moderate or severe CAP, but no benefit compared to monotherapy in nonsevere CAP [19]. Against this, a randomised controlled trial of diagnostic strategy in CAP has demonstrated no statistically significant differences in mortality rate between patients receiving pathogen-directed therapy and patients receiving empirical therapy [103]. Pathogen-directed therapy usually translated into narrow-spectrum monotherapy and, importantly, the frequency of adverse events caused by the antibiotics was much lower in this group. In conclusion, while dual therapy continues to be favoured for severe illness, only good prospective randomised trials will tell us whether there is a real advantage with this approach.

Table 2. Studies recommending combination therapy for patients with community-acquired pneumonia (CAP)

First author [ref.]	Cohort	Site	Outcome	Study design
Gleason [5]	Patients aged ⩾65 years with CAP	Ward	Lower 30-day mortality with β-lactam plus macrolide	Multicentre, retrospective
Dudas [6]	CAP	Ward	Lower mortality with β-lactam plus macrolide and reduced LOS	Multicentre, prospective
Houck [7]	Patients aged ⩾65 years with CAP	Ward	Lower mortality with β-lactam plus macrolide in 1 of 3 years	Multicentre, retrospective
Waterer [8]	Pneumococcal bacteraemia	Ward	Lower hospital mortality with combination	Multicentre, retrospective
Brown [10]	CAP	Ward	Lower 30-day mortality with β-lactam plus macrolide	Multicentre, retrospective
Martínez [9]	Pneumococcal bacteraemia	Ward	Lower in-hospital mortality with β-lactam plus macrolide	Monocentre, retrospective
Baddour [11]	Pneumococcal bacteraemia	Ward/ICU	Lower 14-day mortality with combination	Multicentre, prospective
Weiss [102]	Pneumococcal bacteraemia	Ward	Lower mortality with combination	Monocentre, retrospective
García-Vázquez [12]	CAP	Ward	Lower mortality with β-lactam plus macrolide	Multicentre, prospective
Mortensen [13]	CAP	Ward/ICU	Lower 30-day mortality with β-lactam plus other than fluoroquinolones	Multicentre, retrospective
Rodríguez [14]	CAP	ICU	Lower 28-day mortality with combination	Multicentre, retrospective
Metersky [15]	Pneumococcal bacteraemia	Ward	Lower 30-day mortality with β-lactam plus macrolide	Multicentre, retrospective
Restrepo [16]	Severe sepsis pneumonia	Ward	Lower 30- and 90-day mortalities with combination plus macrolide	Multicentre, retrospective
Tessmer [17]	CAP	Ward	Lower 14- and 30-day mortalities with β-lactam plus macrolide	Multicentre, retrospective
Martín-Loeches [18]	Intubated CAP	ICU	Lower ICU mortality IDSA/ATS combination plus macrolide	Multicentre, prospective
Rodrigo [19]	CAP	Ward	β-lactam/macrolide combination therapy associated with lower 30-day inpatient mortality	Multicentre, retrospective

LOS: length of stay; ICU: intensive care unit; IDSA: Infectious Diseases Society of America; ATS: American Thoracic Society.

What are the current empirical antibiotic guideline recommendations?

Most guidelines stratify empirical antibiotic therapy recommendations according to disease severity, recognising that a different approach may be required for those who are severely ill. This is carried out in different ways in different guidelines. For example, the British Thoracic Society [104] have adopted an approach based on CURB65 (confusion, urea >7 mmol·L^{-1}, respiratory rate $\geqslant 30$ breaths·min^{-1}, blood pressure <90 mmHg (systolic) or $\leqslant 60$ mmHg (diastolic), age $\geqslant 65$ years) score, whereas the European Respiratory Society (ERS)/European Society for Clinical Microbiology and Infectious Diseases (ESCMID) [105] simply specify severe or nonsevere illness and the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines [106] stratify according to site of care.

Table 3. European Respiratory Society/European Society for Clinical Microbiology and Infectious Diseases treatment option for patients hospitalised with community-acquired pneumonia

Aminopenicillin ± macrolide
Aminopenicillin/β-lactamase inhibitor ± macrolide
Non-antipseudomonal cephalosporin
Cefotaxime or ceftriaxone ± macrolide
Levofloxacin
Moxifloxacin
Penicillin G ± macrolide

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ERS/ESCMID recommendations

The ERS/ESCMID recommendations for empirical and antimicrobial treatment for low severity CAP are shown in table 3 [105].

It is worth noting that in providing guidelines for empirical therapy of CAP across Europe, these guidelines need to take account of a number of issues. 1) Microbial causes vary little across Europe, although there is some evidence for a greater importance of severe pneumonia due to GNEB, including *P. aeruginosa*, in southern Europe. 2) Antibiotic resistance is very country specific and mainly occurs at higher frequencies in southern European countries. 3) Current antibiotic practice is country specific and varies with a greater use of narrow-spectrum penicillins in some northern European countries. 4) Availability of particular antibiotic molecules will vary from country to country.

Partly for the reasons above, and partly due to a lack of evidence for the superior effectiveness of any individual antibiotic in randomised controlled trials, the ERS/ESCMID guidelines give a wide range of options for the treatment of nonsevere CAP without giving priority to any particular antibiotic.

The ERS/ESCMID guideline recommendations for severe CAP reflect perceptions of the importance of *P. aeruginosa* in southern European countries (table 4). The incidence of CAP due to *P. aeruginosa* seems to be low overall [83]. In patients with risk factors for *P. aeruginosa*, meropenem offers advantages over imipenem [107]. Patients at risk of CAP due to *P. aeruginosa* should always be treated with two antipseudomonal drugs in order to reduce the chance of inadequate treatment. Ceftazidime has to be combined with penicillin G for coverage of *S. pneumoniae*. In case of ciprofloxacin resistance or intolerability, levofloxacin 750 mg for 24 h or 500 mg twice daily is an alternative and it also covers Gram-positive bacteria if treatment is empirical.

IDSA/ATS recommendations

The current USA guidelines take into consideration potentially unique bacteriological patterns in the USA, particularly focusing on the role of drug-resistant *S. pneumoniae*, atypical pathogens and methicillin-resistant *S. aureus,* which probably explains why the USA recommendations for empirical therapy differ from those in Europe. One of the major differences between USA and European CAP management is the recommendation in USA guidelines that all patients receive empirical therapy not only for *S. pneumoniae* but also for atypical pathogens (table 5). The frequency of these organisms as CAP pathogens has varied in studies, with recent data from North

Table 4. European Respiratory Society/European Society for Clinical Microbiology and Infectious Diseases treatment options for patients hospitalised with severe community-acquired pneumonia

No risk factors for *Pseudomonas aeruginosa*
Non-antipseudomonal cephalosporin ± macrolide (moxifloxacin/levofloxacin)
Risk factors for *Pseudomonas aeruginosa*[#]
Antipseudomonal cephalosporin OR
Acylureidopenicillin with β-lactamase inhibitor OR
Carbapenem (meropenem preferred) PLUS ciprofloxacin OR
Carbapenem (meropenem preferred) PLUS macrolide PLUS aminoglycoside (gentamicin, tobramycin or amikacin)

[#]: patients with two or more of recent hospitalisations, recent antibiotics or more than four courses per year, severe underlying chronic obstructive pulmonary disease and oral steroid use (>10 mg prednisolone per day). Reproduced from [105] with permission from the publisher.

America and elsewhere suggesting that they may be present in up to 60% of CAP episodes, and that they can serve as co-pathogens, along with *S. pneumoniae*, in up to 40% of patients [108–110]. When mixed infection is present, particularly with *Chlamydophila* pneumoniae and pneumococcus, it may lead to a more complex course of illness and a longer length of stay than if a single pathogen is responsible. Whereas atypical pathogens have been thought to be most common in young and healthy individuals, a population study from Ohio, USA [108] showed that they are present in patients of all ages, including the elderly and even those in nursing homes. The importance of atypical pathogens has been suggested by several studies of inpatients from the USA, including those with bacteraemic pneumococcal pneumonia, showing a mortality benefit from therapies including a macrolide or quinolone, agents that would be active against these organisms [8, 10, 11, 111–113]. In one study, the benefit of adding a macrolide only applied if it was added to a cephalosporin but not if it was added to a β-lactam/β-lactamase inhibitor combination [5]. Most of the data on this issue have come from studies of Medicare patients, but at least one large study included nearly 15 000

Table 5. Most common aetiologies of community-acquired pneumonia in the USA

Patient type	Aetiology
Outpatient	*Streptococcus pneumoniae*
	Mycoplasma pneumoniae
	Haemophilus influenzae
	Chlamydophila pneumoniae
	Respiratory viruses
Inpatient, non-ICU	*Streptococcus pneumoniae*
	Mycoplasma pneumoniae
	Chlamydophila pneumoniae
	Haemophilus influenzae
	Legionella spp.
	Aspiration
	Respiratory viruses
Inpatient, ICU	*Streptococcus pneumoniae*
	Staphylococcus aureus
	Legionella spp.
	Gram-negative bacilli
	Haemophilus influenzae

ICU: intensive care unit. Reproduced from [106] with permission from the publisher.

Table 6. Infectious Diseases Society of America/American Thoracic Society recommended empirical antibiotics for community-acquired pneumonia

Outpatient treatment
- Previously healthy and no use of antimicrobials within the previous 3 months:
  - Macrolide (strong recommendation) OR
  - Doxycyline (weak recommendation)
- Presence of comorbidities such as chronic heart, lung, liver or renal disease, diabetes mellitus, alcoholism, malignancies, immunosuppressing conditions or use of antimicrobials within the previous 3 months:
  - Respiratory fluoroquinolone (moxifloxacin, gemifloxacin or levofloxacin OR
  - β-lactam plus a macrolide) (strong recommendation)

Inpatients, non-ICU treatment
- Respiratory fluoroquinolone (strong recommendation) OR
- β-lactam plus a macrolide (strong recommendation)

Inpatients, ICU treatment
- β-lactam (cefotaxime, ceftriaxone or ampicillin-sulbactam) PLUS either azithromycin or a respiratory fluoroquinolone (strong recommendation)[#]

Special concerns
- If *Pseudomonas* is a consideration:
  - An antipneumococcal, antipseudomonal β-lactam (piperacillintazobactam, cefepime, imipenem or meropenem) PLUS either ciprofloxacin or levofloxacin OR
  - The same β-lactam PLUS an aminoglycoside and azithromycin OR
  - The same β-lactam PLUS an aminoglycoside and an anti-pneumococcal fluoroquinolone[¶]
  - If community-acquired methicillin-resistant *Staphylococcus aureus* is a consideration, addition of vancomycin or linezolid is recommended

ICU: intensive care unit. [#]: for penicillin-allergic patients a respiratory fluoroquinolone and aztreonam are recommended; [¶]: for penicillin-allergic patients, substitute aztreonam for above β-lactam. Reproduced from [106] with permission from the publisher.

patients aged <65 years and reached the same conclusions [10]. Atypical organism pneumonia may not be a constant phenomenon, and the frequency of infection may vary over the course of time and with geography (table 6).

The future

CAP will remain a common condition and our ability to predict the causative pathogen is unlikely to improve. Advances in microbiological techniques will need to produce tests that are sensitive, specific, rapid and inexpensive if they are to remove the need for empirical antibiotic therapy. Such tests are purely aspirational at present. Empirical antibiotic therapy is here to stay. Good quality randomised controlled trials are needed to allow us to refine empirical antibiotic recommendations in the future.

Statement of Interest

M. Woodhead was a member of the Pfizer pneumococcal vaccine clinical trial data monitoring committee. He received travel expenses from Bayer for his travel to the ERS 2011 and 2012 Annual Congresses.

References

1. Garau J, Calbo E. Community-acquired pneumonia. *Lancet* 2008; 371: 455–458.
2. Arnold FW, LaJoie AS, Brock GN, *et al.* Improving outcomes in elderly patients with community-acquired pneumonia by adhering to national guidelines: Community-Acquired Pneumonia Organization International cohort study results. *Arch Intern Med* 2009; 169: 1515–1524.
3. Johnstone J, Eurich DT, Minhas JK, *et al.* Impact of the pneumococcal vaccine on long-term morbidity and mortality of adults at high risk for pneumonia. *Clin Infect Dis* 2010; 51: 15–22.
4. Austrian R, Gold J. Pneumococcal bacteremia with special reference to bacteremic pneumococcal pneumonia. *Ann Intern Med* 1964; 60: 759–770.
5. Gleason PP, Meehan TP, Fine JM, *et al.* Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. *Arch Intern Med* 1999; 159: 2562–2572.
6. Dudas V, Hopefl A, Jacobs R, *et al.* Antimicrobial selection for hospitalized patients with presumed community-acquired pneumonia: a survey of nonteaching US community hospitals. *Ann Pharmacother* 2000; 34: 446–452.
7. Houck PM, MacLehose RF, Niederman MS, *et al.* Empiric antibiotic therapy and mortality among Medicare pneumonia inpatients in 10 Western states: 1993, 1995, and 1997. *Chest* 2001; 119: 1420–1426.
8. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. *Arch Int Med* 2001; 161: 1837–1842.
9. Martinez JA, Horcajada JP, Almela M, *et al.* Addition of a macrolide to a β-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis* 2003; 36: 389–395.
10. Brown RB, Iannini P, Gross P, *et al.* Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. *Chest* 2003; 123: 1503–1511.
11. Baddour LM, Yu VL, Klugman KP, *et al.* Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteriemia. *Am J Respir Crit Care Med* 2004; 170: 440–444.
12. García-Vázquez E, Mensa J, Martinez JA, *et al.* Lower mortality among patients with community-acquired pneumonia treated with a macrolide plus a β-lactam agent *versus* a β-lactam agent alone. *Eur J Clin Microbiol Infect Dis* 2005; 24: 190–195.
13. Mortensen EM, Restrepo MI, Anzueto A, *et al.* The impact of empiric antimicrobial therapy with a β-lactam and fluoroquinolone on mortality for patients hospitalized with severe pneumonia. *Crit Care* 2006; 10: R8.
14. Rodríguez A, Mendia A, Sirvent JM, *et al.* Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. *Crit Care Med* 2007; 35: 1493–1498.
15. Metersky ML, Ma A, Houck PM, *et al.* Antibiotics for bacteremic pneumonia: improved outcomes with macrolides but not fluoroquinolones. *Chest* 2006; 131: 466–473.
16. Restrepo MI, Mortensen EM, Waterer GW, *et al.* Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. *Eur Respir J* 2009; 33: 153–159.
17. Tessmer A, Welte T, Martus P, *et al.* Impact of intravenous β-lactam/macrolide *versus* β-lactam monotherapy on mortality in hospitalized patients with community-acquired pneumonia. *J Antimicrob Chemother* 2009; 63: 1025–1033.
18. Martín-Loeches I, Lisboa T, Rodríguez A, *et al.* Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intensive Care Med* 2010; 1025–1033.

19. Rodrigo C, Mckeever TM, Woodhead M, *et al.* Single *versus* combination antibiotic therapy in adults hospitalised with community acquired pneumonia. *Thorax* 2013; 68: 493–495.
20. Woodhead MA, Macfarlane JT. Comparative clinical and laboratory features of legionella with pneumococcal and mycoplasma pneumonias. *Br J Dis Chest* 1987; 81: 133–139.
21. Benenson RS, Kepner AM, Pyle DN, *et al.* Selective use of blood cultures in emergency department pneumonia patients. *J Emerg Med* 2007; 33: 1–8.
22. Afshar N, Tabas J, Afshar K, *et al.* Blood cultures for community-acquired pneumonia: are they worthy of two quality measures? A systematic review. *J Hosp Med* 2009; 4: 112–123.
23. Garcia-Vazquez E, Marcos MA, Mensa J, *et al.* Assessment of the usefulness of sputum culture for diagnosis of community-acquired pneumonia using the PORT predictive scoring system. *Arch Intern Med* 2004; 164: 1807–1811.
24. Signori LG, Ferreira MW, Vieira LC, *et al.* Sputum examination in the clinical management of community-acquired pneumonia. *J Bras Pneumol* 2008; 34: 152–158.
25. Pisoa RJ, Iven-Kollera D, Koller MT, *et al.* The routine use of the urinary pneumococcalantigen test in hospitalised patients with community acquired pneumonia has limited impact for adjustment of antibiotic treatment. *Swiss Med Wkly* 2012; 142: w13679.
26. Falguera M, Ruiz-González A, Schoenenberger JA, *et al.* Prospective, randomised study to compare empirical treatment *versus* targeted treatment on the basis of the urine antigen results in hospitalised patients with community-acquired pneumonia. *Thorax* 2010; 65: 101–106.
27. Ewig S, Bauer T, Hasper E, *et al.* Value of routine microbial investigation in community-acquired pneumonia treated in a tertiary care center. *Respiration* 1996; 63: 164–169.
28. Woodhead MA, Arrowsmith J, Chamberlain-Webber R, *et al.* The value of routine microbial investigation in community acquired pneumonia. *Respir Med* 1991; 85: 313–317.
29. Lung M, Rello J. Microbiology of bacterial CAP using traditional and molecular techniques. *In:* Chalmers JD, Pletz MW, Aliberti S, eds. Community-Acquired Pneumonia. *Eur Respir Monogr* 2014; 63: 25–41.
30. Welker JA, Huston M, McCue JD. Antibiotic timing and errors in diagnosing pneumonia. *Arch Intern Med* 2008; 168: 351–356.
31. Battleman DS, Callahan M, Thaler HT. Rapid antibiotic delivery and appropriate antibiotic selection reduce length of hospital stay of patients with community-acquired pneumonia: link between quality of care and resource utilization. *Arch Intern Med* 2002; 162: 682–688.
32. Silber SH, Garrett C, Singh R, *et al.* Early administration of antibiotics does not shorten time to clinical stability in patients with moderate-to-severe community-acquired pneumonia. *Chest* 2003; 124: 1798–1804.
33. Waterer GW, Kessler LA, Wunderink RG. Delayed administration of antibiotics and atypical presentation in community-acquired pneumonia. *Chest* 2006; 130: 11–15.
34. Meehan TP, Fine MJ, Krumholz HM, *et al.* Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA* 1997; 278: 2080–2084.
35. Cheng AC, Buising KL. Delayed administration of antibiotics and mortality in patients with community-acquired pneumonia. *Ann Emerg Med* 2009; 53: 618–624.
36. Bruns AH, Oosterheert JJ, Hustinx WM. Time for first antibiotic dose is not predictive for the early clinical failure of moderate–severe community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis* 2009; 28: 913–919.
37. Metersky ML, Sweeney TA, Getzow MB, *et al.* Antibiotic timing and diagnostic uncertainty in Medicare patients with pneumonia. Is it reasonable to expect all patients to receive antibiotics within 4 hours. *Chest* 2006; 130: 16–21.
38. Kanwar M, Brar N, Khatib R, *et al.* Misdiagnosis of community acquired pneumonia and inappropriate utilizations of antibiotics: side effects of the 4-hour antibiotic administration rule. *Chest* 2007; 131: 1865–1869.
39. Yu KT, Wyer PC. Evidence behind the 4-hour rule for initiation of antibiotic therapy in community-acquired pneumonia. *Ann Emerg Med* 2008; 51: 651–662.
40. Kollef MH, Sherman G, Ward S, *et al.* Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999; 115: 462–474.
41. Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. *Mayo Clin Proc* 2011; 86: 156–167.
42. Berjohn CM, Fishman NO, Joffe MM, *et al.* Treatment and outcomes for patients with bacteremic pneumococcal pneumonia. *Medicine (Baltimore)* 2008; 87: 160–166.
43. Houck PM, Bratzler DW, Nsa W, *et al.* Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med* 2004; 164: 637–644.
44. Lee JS, Primack BA, Mor MK, *et al.* Processes of care and outcomes for community-acquired pneumonia. *Am J Med* 2011; 124: 1175.
45. Waterer GW, Kessler LA, Wunderink RG. Delayed administration of antibiotics and atypical presentation in community-acquired pneumonia. *Chest* 2006; 130: 11–15.
46. Wilson PA, Wilson JF. Severe community-acquired pneumonia: an Australian perspective. *Int Med J* 2005; 35: 699–705.
47. Simonetti A, Viasus D, Garcia-Vidal C, *et al.* Timing of antibiotic administration and outcomes of hospitalized patients with community-acquired and healthcare-associated pneumonia. *Clin Microbiol Infect* 2012; 18: 1149–1155.

48. Dellinger RP, Levy MM, Rhodes A, *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; 39: 165–228.
49. Romero Pizarro Y, Bascuñana Morejón de Girón J, Vicuña Andrés I. Tiempo hasta la administracion de la primera dosis de antibiotico en las neumonias adquiridas en la comunidad en un Servicio de Urgencias Hospitalario [Time to first antibiotic dose in community-acquired pneumonia diagnosed in an emergency department]. *Rev Clin Esp* 2009; 209: 409–414.
50. Querol-Ribelles JM, Tenías JM, Forés R, *et al.* Demora del tratamiento antibiotico y evolucion de los pacientes con neumonia adquirida en la comunidad que requieren hospitalizacion [Antibiotic treatment onset delay and clinical evolution in admitted patients with community-acquired pneumonia]. *Med Clin (Barc)* 2008; 130: 366–370.
51. LiverTox. Drug record amoxicillin-clavulanate. Bethesda, US National Library of Medicine. Available from http://livertox.nih.gov/AmoxicillinClavulanate.htm Date last updated: November 5, 2013.
52. Mao JC, Robishaw EE. Erythromycin, a peptidyltransferase effector. *Biochem* 1972; 11: 4864–4872.
53. Vazquez D. The macrolide antibiotics. *In:* Corcoran, JW, Hahn FE, eds. Antibiotics III. Mechanism of Action of Antimicrobial and Antitumor Agents. Berlin, Springer-Verlag, 1975; pp. 459–479.
54. Menninger JR, Otto DP. Erythromycin, carbomycin, and spiramycin inhibit protein synthesis by stimulating the dissociation of peptidyl-tRNA from ribosomes. *Antimicrob Agents Chemother* 1982; 21: 810–818.
55. Champney WS, Burdine R. Macrolide antibiotics inhibit 50S ribosomal subunit assembly in *Bacillus subtilis* and *Staphylococcus aureus*. *Antimicrob Agents Chemother* 1995; 39: 2141–2144.
56. Salih W, Short PM, Schembri S. Macrolides as anti-inflammatory agents in CAP. *In:* Chalmers JD, Pletz MW, Aliberti S, eds. Community-Acquired Pneumoina. *Eur Respir Monogr* 2014; 63: 243–255.
57. Malhotra-Kumar S, Lammens C, Coenen S, *et al.* Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet* 2007; 369: 482–490.
58. Tellier G, Niederman MS, Nusrat R, *et al.* Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. *J Antimicrob Chemother* 2004; 54: 515–523.
59. Mathers DL, Hassman J, Tellier G. Efficacy and tolerability of once daily oral telithromycin compared with clarithromycin for the treatment of community-acquired pneumonia in adults. *Clin Ther* 2004; 26: 48–62.
60. Pullman J, Champlin J, Vrooman PS Jr. Efficacy and tolerability of once-daily oral therapy with telithromycin compared with trovafloxacin for the treatment of community-acquired pneumonia in adults. *Int J Clin Pract* 2003; 57: 377–384.
61. Hagberg L, Carbon C, van Rensburg DJ, *et al.* Telithromycin in the treatment of community-acquired pneumonia: a pooled analysis. *Respir Med* 2003; 97: 625–633.
62. Brinker AD, Wassel RT, Lyndly J, *et al.* Telithromycin-associated hepatotoxicity: clinical spectrum and causality assessment of 42 cases. *Hepatology* 2009; 49: 250–257.
63. Hooper D. Quinolones. *In:* Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases. 5th Edn. Philadelphia, Churchill Livingstone, 2000; pp. 404–423.
64. Hooper DC, Wolfson JS. Mechanisms of quinolone action and bacterial killing. *In:* Quinolone Antimicrobial Agents. 2nd Edn. Washington, American Society for Microbiology, 1993; pp. 53–57.
65. Lodise TP, Kwa A, Cosler L, *et al.* Comparison of beta-lactam and macrolide combination therapy *versus* fluoroquinolonemonotherapy in hospitalized Veterans Affairs patients with community-acquired pneumonia. *Antimicrob Agents Chemother* 2007; 51: 3977–3982.
66. Dartois N, Castaing N, Gandjini H, *et al.* Tigecycline *versus* levofloxacin for the treatment of community-acquired pneumonia: European experience. *J Chemother* 2008; 20: 28–35.
67. Lin TY, Lin SM, Chen HC, *et al.* An open-label, randomized comparison of levofloxacin and amoxicillin/clavulanate plus clarithromycin for the treatment of hospitalized patients with community-acquired pneumonia. *Chang Gung Med J* 2007; 30: 321–332.
68. Portier H, Brambilla C, Garre M, *et al.* Moxifloxacin monotherapy compared to amoxicillin-clavulanate plus roxithromycin for nonsevere community-acquired pneumonia in adults with risk factors. *Eur J Clin Microbiol Infect Dis* 2005; 24: 367– 376.
69. Querol-Ribelles JM, Tenias JM, Querol-Borras JM, *et al.* Levofloxacin *versus* ceftriaxone plus clarithromycin in the treatment of adults with community-acquired pneumonia requiring hospitalization. *Int J Antimicrob Agents* 2005; 25: 75–83.
70. Salkind AR, Cuddy PG, Foxworth JW. Fluoroquinolone treatment of community-acquired pneumonia: a meta-analysis. *Ann Pharmacother* 2002; 36: 1938–1943.
71. Schein J, Janagap-Benson C, Grant R, *et al.* A comparison of levofloxacin and moxifloxacin use in hospitalized community-acquired pneumonia (CAP) patients in the US: focus on length of stay. *Curr Med Res Opin* 2008; 24: 895–906.
72. Tanaseanu C, Bergallo C, Teglia O, *et al.* Integrated results of 2 phase 3 studies comparing tigecycline and levofloxacin in community-acquired pneumonia 509. *Diagn Microbiol Infect Dis* 2008; 61: 329–338.
73. Tanaseanu C, Milutinovic S, Calistru PI, *et al.* Efficacy and safety of tigecycline *versus* levofloxacin for community-acquired pneumonia. *BMC Pulm Med* 2009; 9: 44.

74. Torres A, Muir JF, Corris P, *et al.* Effectiveness of oral moxifloxacin in standard first-line therapy in community-acquired pneumonia. *Eur Respir J* 2003; 21: 135–143.
75. Vardakas KZ, Siempos II, Grammatikos A, *et al.* Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials. *CMAJ* 2008; 179: 1269–1277.
76. Scott-Levin physician drug and diagnosis audit, November 2000–January 2001. Newtown, PA, Scott-Levin, 2001.
77. Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. *Drug Saf* 2009; 32: 359–378.
78. Bergallo C, Jasovich A, Teglia O, *et al.* Safety and efficacy of intravenous tigecycline in treatment of community-acquired pneumonia: results from a double-blind randomized phase 3 comparison study with levofloxacin. *Diagn Microbiol Infect Dis* 2009; 63: 52–61.
79. Ortiz-Ruiz G, Vetter N, Isaacs R, *et al.* Ertapenem *versus* ceftriaxone for the treatment of community acquired pneumonia in adults: combined analysis of two multicentre randomized, double-blind studies. *J Antimicrob Chemother* 2004; 53: Suppl. 2, ii59–ii66.
80. Vetter N, Cambronero-Hernandez E, Rohlf J, *et al.* A prospective, randomized, double-blind multicenter comparison of parenteral ertapenem and ceftriaxone for the treatment of hospitalized adults with community-acquired pneumonia. *Clin Ther* 2002; 24: 1770–1785.
81. Yakovlev SV, Stratchounski LS, Woods GL, *et al.* Ertapenem *versus* cefepime for initial empirical treatment of pneumonia acquired in skilled-care facilities or in hospitals outside the intensive care unit. *Eur J Clin Microbiol Infect Dis* 2006; 25: 633–641.
82. Murcia JM, Gonzalez-Comeche J, Marin A, *et al.* Clinical response to ertapenem in severe community-acquired pneumonia: a retrospective series in an elderly population. *Clin Microbiol Infect* 2009; 15: 1046–1050.
83. von Baum H, Welte T, Marre R, *et al.* Community-acquired pneumonia through *Enterobacteriaceae* and *Pseudomonas aeruginosa*: diagnosis, incidence and predictors. *Eur Respir J* 2010; 35: 598–605.
84. Mills GD, Oehley MR, Arrol B. Effectiveness of beta lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis. *BMJ* 2005; 330: 456.
85. Frei CR, Koeller JM, Burgess DS, *et al.* Impact of atypical coverage for patients with community-acquired pneumonia managed on the medical ward: results from the United States Community-Acquired Pneumonia Project. *Pharmacotherapy* 2003; 23: 1167–1174.
86. Lui G, Ip M, Lee N, *et al.* Role of ''atypical pathogens'' among adult hospitalized patients with community-acquired pneumonia. *Respirology* 2009; 14: 1098–1105.
87. Shefet D, Robenshtock E, Paul M, *et al.* Empiric antibiotic coverage of atypical pathogens for community acquired pneumonia in hospitalized. *Cochrane Database Syst Rev* 2005; 2: CD004418.
88. Cillóniz C, Ewig S, Polverino E. Microbial aetiology of community-acquired pneumonia and its relation to severity. *Thorax* 2011; 66: 340–346.
89. Capelastegui A, España PP, Bilbao A, *et al.* Etiology of community-acquired pneumonia in a population-based study: link between etiology and patients characteristics, process-of-care, clinical evolution and outcomes. *BMC Infectious Dis* 2012; 12: 134.
90. Lim I, Shaw DR, Stanley DP, *et al.* A prospective hospital study of the aetiology of community-acquired pneumonia. *Med J Aust* 1989; 151: 87–91.
91. Owens RC Jr, Donskey CJ, Gaynes RP, *et al.* Antimicrobial-associated risk factorsfor *Clostridium difficile* infection. *Clinic Infect Disease* 2008; 46: Suppl. 1, S19–S31.
92. Tacconelli E, De Angelis G, Cataldo MA, *et al.* Does antibiotic exposure increase the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) isolation? Asystematic review and meta-analysis. *J Antimicrob Chemother* 2008; 61: 26–38.
93. Woodhead M, Welch CA, Harrison DA, *et al.* Community-acquired pneumonia on the intensive care unit: secondary analysis of 17,869 cases in the ICNARC Case Mix Programme Database. *Crit Care* 2006; 10: Suppl. 2, S1.
94. Royal College of Physicians. Acute medical care. The right person, in the right setting – first time. Report of the Acute Medicine Task Force. London, Royal College of Physicians, 2007.
95. Paganin F, Lilienthal F, Bourdin A, *et al.* Severe community-acquired pneumonia: assessment of microbial aetiology as mortality factor. *Eur Respir J* 2004; 24: 779–785.
96. Huang HH, Zhang YY, Xiu QY, *et al.* Community-acquired pneumonia in Shanghai, China: microbial etiology and implications for empirical therapy in a prospective study of 389 patients. *Eur J Clin Microbiol Infect Dis* 2006; 25: 369–374.
97. Leroy O, Vandenbussche C, Coffinier C, *et al.* Community-acquired aspiration pneumonia in intensive care units. Epidemiological and prognosis data. *Am J Respir Crit Care Med* 1997; 156: 1922–1929.
98. Maimon N, Nopmaneejumruslers C, Marras TK. Antibacterial class is not obviously important in outpatient pneumonia: a meta-analysis. *Eur Respir J* 2008; 31: 1068–1076.
99. Iannini PB, Paladino JA, Lavin B, *et al.* A case series of macrolide treatment failures in community acquired pneumonia. *J Chemother* 2007; 19: 536–545.
100. Rzeszutek M, Wierzbowski A, Hoban DJ, *et al.* A review of clinical failures associated with macrolide-resistant *Streptococcus pneumoniae. Int J Antimicrob Agents* 2004; 24: 95–104.
101. Weiss K, Low DE, Cortes L, *et al.* Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic *Streptococcus pneumoniae* in adults. *Can Respir J* 2004; 11: 589–593.

102. Paul M, Nielsen AD, Gafter-Gvili A, *et al.* The need for macrolides in hospitalised community-acquired pneumonia: propensity analysis. *Eur Respir J* 2007; 30: 525–531.
103. Van der Eerden MM, Vlaspolder F, de Graaff CS, *et al.* Comparison between pathogen directed antibiotic treatment and empirical broad spectrum antibiotic treatment in patients with community acquired pneumonia: a prospective randomised study. *Thorax* 2005; 60: 672–678.
104. Lim WS, Baudoin SV, George RC, *et al.* BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; 64: Suppl. 3, iii1–iii552.
105. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections. *Clin Microbiol Infect* 2011; 17: E1–E59.
106. Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44: Suppl. 2, S27–S72.
107. Romanelli G, Cravarezza P, Pozzi A, *et al.* Carbapenems in the treatment of severe community-acquired pneumonia in hospitalized elderly patients: a comparative study against standard therapy. *J Chemother* 2002; 14: 609–617.
108. Marston BJ, Plouffe JF, File TM Jr. Incidence of community-acquired pneumonia requiring hospitalization: results of a population-based active surveillance Study in Ohio. The Community-Based Pneumonia Incidence Study Group. *Arch Intern Med* 1997; 157: 1709–1718.
109. Lieberman D, Schlaeffer F, Boldur I. Multiple pathogens in adult patients admitted with community-acquired pneumonia: a one year prospective study of 346 consecutive patients. *Thorax* 1996; 51: 179–184.
110. Marrie TJ, Peeling RW, Fine MJ, *et al.* Ambulatory patients with community-acquired pneumonia: the frequency of atypical agents and clinical course. *Am J Med* 1996; 101: 508–515.
111. Leroy O, Saux P, Bédos JP, *et al.* Comparison of levofloxacin and cefotaxime combined with ofloxacin for ICU patients with community-acquired pneumonia. *Chest* 2005; 128: 172–183.
112. Weiss K, Tillotson GS. The controversy of combination *vs.* monotherapy in the treatment of hospitalized community-acquired pneumonia. *Chest* 2005; 128: 940–946.
113. Mufson MA, Sanek RJ. Bacteremic pneumococcal pneumonia in one American city: a 20 year longitudinal study, 1978–1997. *Am J Med* 1999; 107: 34S–43S.

Chapter 12

Antibiotic choice, route and duration: minimising the harm associated with antibiotics

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SUMMARY: Antibiotics are the cornerstone of treatment in community-acquired pneumonia (CAP), and scientific societies deliver updated recommendations regarding choice and duration. Initial severity, patient's characteristics and site of care are key for initial decisions, whereas stability influences switching of route and duration of treatment. Clinical objective criteria for switching therapy have been proved safe for patient outcome, beneficial for reducing antibiotic pressure, and cost saving. Strategies for early switch therapy are included in guidelines although a better implementation through predefined criteria and/or clinical pathways is warranted. Earlier switching is related to shorter duration of treatment and length of hospital stay. Recent meta-analyses have demonstrated no negative outcomes with shorter courses ($\leqslant$7 days) in mild-to-moderate episodes while fewer studies are available in severe CAP. Biomarkers appear to be useful for customising the total duration of antibiotic treatment. Most recent recommendations have reduced the duration of treatment to 5–7 days.

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During the past decades, different scientific medical societies have issued and updated evidence-based guidelines for the management of community-acquired pneumonia (CAP). The most widespread guidelines are those published by the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) [1], by the British Thoracic Society (BTS) [2], and the European Respiratory Society (ERS)/European Society of Clinical Microbiology and Infectious Diseases [3].

The goals of guidelines are mainly to improve healthcare practice and outcomes, reduce morbidity and mortality, recommend prevention strategies and control costs in order to achieve cost-effective management. In fact, several studies have proved that compliance with guidelines recommendations, mainly with regard to all components of antibiotic treatment, is associated with better survival and even with reducing costs [4, 5].

Antibiotics are the cornerstone of CAP treatment and have greatly reduced its mortality. However, one important consequence of their use is the emergence of resistant microorganisms. Antibiotics cause selective pressure over microorganisms promoting the selection of resistant strains and the acquisition of new resistance mechanisms, thus spreading resistance. The objective of an adequate antibiotic treatment in infection, specifically in CAP, could be expressed as follows "enough antibiotics to get rid of pathogenic microorganisms but not excessive or longer than needed in order to limit the emergence of resistance".

In this chapter several topics related to adequate use of antibiotics will be addressed, concerning route, switch to oral therapy, streamlining and duration of therapy. The evidence and the most important publications will be reviewed along with society recommendations. The last topic updates the state-of-the-art concerning biomarkers usefulness to determine optimal duration of antibiotic therapy and route switching, through the monitoring of serum levels in order to customise treatment.

Route and duration of antibiotic therapy in CAP

Guidelines recommendations: ERS, BTS and ATS

The adequate use of antibiotics as the cornerstone of CAP treatment is probably one of the main reasons for scientific societies to develop evidence-based recommendations. The first crucial decision at diagnosis of CAP is the choice of empiric treatment and route. A description of the generic levels of evidence and guideline statements grades currently used by societies are as follows. Evidence level 1a: good recent systematic review of studies designed to answer the question of interest; evidence level 1b: one or more rigorous studies but not formally combined; evidence level 2: one or more prospective clinical studies which illuminate but do not rigorously answer the question; evidence level 3: one or more retrospective clinical studies; evidence level 4a: formal combination of expert views; and evidence level 4b: other information [2].

The initial route for antibiotic therapy mainly depends on initial severity, patient's conditions and treatment setting/site of care. The general recommendation in guidelines is that oral antibiotics can be used for ambulatory patients from the beginning while intravenous (*i.v.*) treatment is preferred for hospitalised patients [6, 7]. Some carefully selected hospitalised patients may also be considered candidates for exclusively oral treatment [3], whereas patients with severe CAP should always receive *i.v.* medication (at least within the initial hours following admission), with daily evaluation for switching to oral medication as soon as possible (evidence level 4b) [2, 3, 8].

The optimal duration of antibiotic treatment in CAP is still not known, although there are several factors that clinicians should consider, such as severity of episode, causal microorganisms, the presence of bacteraemia [9] and clinical response. Guidelines currently recommend shorter courses of antibiotics, based on two reasons. First, the overuse and prolongation of antibiotic therapy leads to excessive pressure promoting resistance to antibiotics, an impact on endogenous flora and potentially severe side-effects such as *Clostridium difficile* infection [10]. Secondly, several studies have shown that reducing the duration of treatment has not had adverse consequences in CAP resolution. These reasons highlight that shorter courses are a good strategy to minimise harm related to antibiotic use.

The use of objective criteria to assess stability and clinical response allows for a customised antibiotic regimen: shorter courses if early and appropriate responses and longer courses if response is delayed or in case of complications [11]. However, it is not only the host and microorganisms' factors that play an important role; the pharmacokinetics of antibiotics may also determine total duration. Azithromycin is administered for a shorter time due to its long intracellular half-life in respiratory tissues (persists for 3–4 days after completion of therapy), while other antibiotics have different action times [1, 12, 13].

The most recent ERS recommendations suggest that the standard antibiotic treatment duration is 5–7 days (5 days as a minimum and should not exceed 8 days in responding patient) [3].

Table 1. Guidelines for community-acquired pneumonia (CAP) treatment: duration of antibiotic therapy

Source	Recommended duration of therapy	Evidence/ recommendation
IDSA/ATS [1]	Minimum of 5 days, afebrile for 48–72 h and not more than one CAP-associated sign of clinical instability before discontinuation of therapy	1, 2
	Longer duration of therapy if: initial therapy was not active against the identified pathogen; and CAP complicated by extrapulmonary infection (meningitis or endocarditis)	3
BTS [2]	Mild or moderate and uncomplicated pneumonia: 7 days of appropriate antibiotics	4a
	Severe microbiologically undefined pneumonia: 7–10 days of appropriate antibiotics	4a
	Severe CAP with suspected or isolated specific microorganisms (*S. aureus*, Gram-negative enteric bacilli): 14–21 days of appropriate antibiotics	4a
Woodhead and co-workers [3, 14], **Niederman** [15]	*S. pneumoniae* CAP: 7 days (in mild cases) to 10 days (in more severe cases) of appropriate antibiotics	4
	Atypical bacteria and *Legionella* CAP: 10–14 days of appropriate antibiotics	4
	S. aureus or Gram-negative pathogens CAP: 14–21 days of appropriate antibiotics	4

IDSA: Infectious Diseases Society of America; ATS: American Thoracic Society; BTS: British Thoracic Society; *S. aureus*: *Staphylococcus aureus*; *S. pneumoniae*: *Streptococcus pneumoniae*.

IDSA/ATS guidelines recommended that patients with mild and moderate CAP should be treated until they remain afebrile for >48 h, ensuring that not more than one sign of instability or complication is present (evidence level 1) (table 1) [1].

Prolonged duration of antibiotic treatment is more suitable in severe CAP [1–3, 16] and in some specific circumstances such as persistent fever (>72 h), more than one instability criteria, inadequate initial antibiotic and/or presence of extrapulmonary infectious complications (meningitis or endocarditis) (evidence level 3) [1, 16]. Furthermore, updated ERS guidelines [3] also recommend extending antibiotic treatment (14 days) if some microorganisms have been identified, such as intracellular pathogens (with slow response to treatment) or *Legionella* spp. (evidence level 4). A similar recommendation has been made by the IDSA/ATS [1] for some specific aetiologies including: *Staphylococcus aureus* bacteraemia, unusual aetiology (*Pseudomonas aeruginosa*, *Burkholderia pseudomallei*), endemic fungi, and/or for complications such as the presence of empyema, new pulmonary cavities or tissue necrosis (table 1).

Long- *versus* short-course duration of antibiotic therapy: pros and cons

For a long time CAP has been treated with long courses of antibiotics (14 days), although newer guidelines recommend shortening the duration of therapy [17]. This is based on evidence provided by some observational and randomised studies demonstrating no negative effects on outcome. In fact, beneficial effects have been found with short-courses related to both clinical and economic aspects. Fewer days of antibiotic treatment are associated with reduced resistance promoted by antimicrobials [18, 19] and reduced side-effects of drugs [9]. Lode [20] described the adverse events associated with antimicrobials used in respiratory infections. Thus, amoxicillin is ranked as the antibiotic with the most frequent side-effects. Comparing all the different classes of antibiotics, sulfonamides were associated with a clinically higher rate of moderate-to-severe allergic reactions, while sulfonamides and fluoroquinolones were associated with a low but clinically higher rate of neurological or psychiatric disturbances. Most of the antimicrobials caused gastrointestinal disturbances, allergic reactions and *C. difficile*-associated colitis [20]. Moreover,

antibiotic regimens with once-daily dosing along with short-course regimens (⩽7 days) are more likely to enhance compliance [19, 21, 22], and this is feasible with antibiotics with good tissue penetration and high drug concentrations in the infected organ [18].

Three meta-analyses and some randomised controlled trials [9, 18, 23, 24] have compared short-course *versus* extended-course antibiotic regimens and their impact on patient outcome. The main findings pinpointed more benefits than drawbacks in shortening duration of treatment (table 2). The meta-analysis of LI *et al.* [25] included studies with outpatients and mild-to-moderate CAP hospitalised patients (1995 to 2004) with a wide age range treated with the most important antibiotic classes (macrolides, fluoroquinolones and β-lactams). The authors concluded that there were no significant differences with regard to clinical outcomes, mortality, bacteriological eradication and adverse events in those who received short courses (⩽7 days) of antibiotics [25]. HAYASHI *et al.* [23] performed a broader meta-analysis with studies from 1999 to 2007 and confirmed that antibiotic regimens of 5 days are as effective and safe as longer courses [26–30]. The antibiotic group most extensively included in meta-analyses was that of macrolides, which are well known for their longer effect. Interestingly, EL MOUSSAOUI *et al.* [31] performed a randomised controlled trial and showed that a 3-day *i.v.* course with amoxicillin may be as successful as an 8-day course in patients with mild-to-moderate CAP, with non-inferiority in clinical and radiological success. Despite these results, the conclusions do not apply to the population with severe CAP and the sample size is not sufficient. Additional trials have to confirm the non-inferiority of shortening the antibiotic duration [31].

The drawbacks of short antibiotic courses might be related to the risk of relapse or treatment failure due to insufficient antibiotics, as it may occur in patients with severe CAP, those with bacteraemia and specific microorganisms, and/or complications. In fact, despite some evidence proving good outcome results for ⩽7 days of antibiotics compared to >7 days, there are a lack of studies evaluating severe CAP. Although CHOUDHURY *et al.* [32] designed a study in severe CAP (CURB65 score (confusion, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) or ⩽60 mmHg (diastolic), age ⩾65 years) of 3–5) and found good outcomes, they excluded patients admitted to the intensive care unit and those with empyema, bacteraemia or complicated CAP, therefore precluding recommendations for those

Table 2. Meta-analyses: short-course (⩽7 days) *versus* long-course (>7 days) of community-acquired pneumonia antibiotic therapy

First author [ref.]	Antibiotic class and course	Trials n	Patients n	Results
LI [25]	Macrolides: 3 days *versus* 10 days	6	707	No difference in treatment failure or in clinical outcomes
	Macrolides: 5 days *versus* 10 days	5	918	
	Quinolones: 5–7 days *versus* 10 days	2	848	
	Cephalosporins: 5–7 days *versus* 10 days	2	296	
DIMOPOULOS [24]	Macrolides: 5 days *versus* 7 days	1	559	No difference in clinical response, outcomes or mortality
	Quinolones: 5 days *versus* 7 days	1	510	
	Cephalosporins: 5–7 days *versus* 10 days	2	342	
	Amoxicillin: 3 days *versus* 8 days	1	119	
HAYASHI [23]	Macrolides: 5–7 days *versus* 7–10 days	2	937	No difference in clinical radiological or outcome
	Quinolones: 5–7 days *versus* 7–10 days	4	1507	
	Cephalosporins: 5–7 days *versus* 10 days	2	296	
	Amoxicillin: 3 days *versus* 8 days	1	119	

specific populations. To conclude, the latest ERS guidelines [3] suggest that although most patients hospitalised with nonsevere pneumonia are appropriately treated with a 7-day course of antibiotic, it appears reasonable that treatment duration in severe pneumonia should be prolonged. The isolation of some specific microorganisms, such as *P. aeruginosa* and/or other nonfermenters, may pose an increased risk of relapse with short courses [3].

Early switch: from *i.v.* to oral route of antibiotic therapy

Definition and aims of the switch therapy

The *i.v.* route has been considered the preferred route in CAP patients with severe infection who need hospitalisation, since it achieves higher and, remarkably, faster drug concentrations. Moreover, severe CAP patients may present haemodynamic instability and, quite often, low consciousness and oral intake problems at admission. Thus, they are suitable to receive *i.v.* treatment although there is no scientific evidence to maintain this route for the entire length of stay.

In the 1980s the ''switch antibiotic therapy'' strategy was suggested in order to substitute the *i.v.* route with the oral route. The benefits of this approach in the management of hospitalised patients are multiple. 1) Economics: to reduce direct costs of the *i.v.* compared to the oral formulations, and indirect costs, facilitating earlier discharge; 2) safety: to decrease adverse effects of *i.v.* lines and drugs; 3) convenience: to ameliorate comfort and mobility of patients; and 4) pharmacodynamics: to take advantage of the high bioavailability of the new oral antimicrobials [33]. Although the optimal time is not perfectly known, several studies have shown that when clinical stability is achieved, switching to oral therapy with an equivalent antibiotic (high bioavailability) is suitable and achieves similar outcomes (table 3).

Streamlining therapy

Another concept usually considered when switching is streamlining antibiotic therapy. That concept relates to de-escalation from an initial empiric broad-spectrum antibiotic to a narrower one. The rationale would be to reduce and adjust antibiotics after an empiric and conservative broad-spectrum regimen (to cover for pneumococcal resistance and mixed infection) once clinical stability is achieved and/or microbiological diagnosis is available.

The goal of a narrower spectrum would be minimising the resistance promoted by antibiotics; it may also reduce the appearance of *C. difficile* and other adverse antibiotic effects. This therapeutic strategy also has the advantage of reducing treatment costs. Scientific societies, such as the ERS, IDSA/ATS and BTS, do not provide specific recommendations concerning de-escalation. In fact, there are limited studies on this specific topic.

The decision to initiate streamlining would rely on clinical response, *i.e.* stability, along with microbiological results, as a more targeted and specific antibiotic could be the best option. One study found a benefit in outcome in severe bacteraemic pneumococcal CAP when using dual antibiotic therapy (at least 48 h of combined antibiotics) [35]. The author suggests that dual antibiotic treatment may be more decisive on prognosis than narrowing the antibiotic spectrum [35]. However, that study was not designed for that specific goal and it remains unclear how long dual therapy is needed for before de-escalation.

Table 3. Oral antibiotic characteristics to consider for therapy switch

Similar antimicrobial spectrum
High bioavailability
Pharmacokinetic characteristics: oral route, administration every 12–24 h
Good tolerance (especially gastrointestinal)
Low resistance selection
Low costs

Modified from [34].

In a randomised controlled study in pneumococcal CAP, diagnosed based on a positive urinary antigen result, FALGUERA *et al.* [36] found that a targeted and reduced spectrum had a negative impact on outcome (more relapses) compared to empirical treatment. This could be because streamlining was performed even before clinical stability was reached or because the study group was rather small. Another important limitation to consider in targeted aetiological treatment is that mixed infections, mainly with atypicals, could be underestimated. In fact, a negative result of urinary *Legionella* antigen may overlook that aetiology, as the test does not have a very high sensitivity and only identifies *Legionella pneumophila* type I.

Thus, a shortcoming is the reduction of efficacy compared to combined therapy in severe infections, in underestimated mixed aetiologies and in severe episodes of CAP with bacteraemia or sepsis. In fact, reluctance of prescribers to de-escalate has been reported when the microorganism involved is unknown and the clinical course is improving [37]. The debate on streamlining therapy in CAP is still open, with scarce studies, while more information has been reported in ventilator-associated pneumonia [38].

Time to switch antibiotic therapy

CAP guidelines strongly recommend switching from *i.v.* to oral antibiotic therapy as soon as the clinical patient's condition permits [1, 2]. Oral antibiotic therapy may be considered in those patients with adequate oral intake, signs of haemodynamic stability, clinical improvement and when fever has resolved for a period of 24 h (evidence level 2) [1]. ERS guideline recommendations suggest that oral switching should be guided by the resolution of the most prominent clinical features at admission or by clinical stability, even in patients with severe pneumonia [3].

Several studies evaluating early switching used a set of clinical stability criteria (table 4) that have been proved safe, without adverse outcomes [38–40]. Approximately 70% of hospitalised patients with CAP are possible candidates for switching therapy after 72 h of *i.v.* antibiotic treatment when clinical stability criteria are achieved [41]. In a multicentre randomised trial, OOSTERHEERT *et al.* [42] demonstrated that, even in severe pneumonia, the median length of time for switching was 3.6 days compared to 7 days in the standard-care control group, without negative impact on outcome and with a safe reduction of length of hospital stay. It remains unclear if all the items included in stability criteria have identical impact for clinical decisions and, in fact, some authors use different combinations of parameters and cut-off points.

However, the persistence of fever, tachypnoea and oxygen requirements are clinical barriers for early switching, as they are considered clinical parameters of instability. In a prospective study investigating barriers for early oral switching, ENGEL *et al.* [43] reported several types and causes for limitations in clinical practice. Interestingly, the authors reported that many physicians were not aware of the guideline advice [43]. Other reasons were misconceptions of the healthcare staff, as well as practical considerations and organisational factors in hospitals, which also played an important role.

A simple proposal for early switching has been made by CASTRO-GUARDIOLA *et al.* [44], who suggested oral switching on a predetermined day (third day) regardless of clinical stability. More studies are necessary to consider this proposal since the vast majority of the studies took into account the stability criteria to switch from *i.v.* to oral therapy.

Oral antibiotics recommended on completion of *i.v.* therapy

The general rule is to switch from the parenteral to oral route with the same class of drug if feasible. In clinically responding patients, it seems logical to maintain the antibiotic type, since most *i.v.* antibiotics have equivalent and effective oral formulations (evidence level 4a) [1, 2, 15]. Nevertheless, the ''switching therapy'' strategy could also be looked upon as an opportunity

for therapeutic de-escalation, reducing the broad spectrum of the initially administered *i.v.* empiric antibiotic [2, 33].

Table 4. Stability criteria used in clinical practice to switch to oral antibiotic therapy

Temperature <37.2°C
Heart rate ⩽100 beats·min^{-1}
Respiratory rate ⩽24 breaths·min^{-1}
Systolic blood pressure ⩾90 mmHg
Arterial oxygen saturation ⩾90% or P_{O_2} ⩾60 mmHg on room air
Oral intake and correct gastro-intestinal absorption
Normal mental status

P_{O_2}: partial pressure of oxygen. Modified from [39].

The selection of the appropriate oral equivalent drug is not always a simple task when de-escalation strategies or earlier switching are considered. In fact, the BTS guideline recommendations suggest that the pharmacist may play an important role in assisting clinicians to select the best switch antibiotic available in each hospital [2]. While some antibiotics (quinolones, macrolides, metronidazole and clindamycin) may be used in both the *i.v.* and oral route, due to their bioavailability and pharmacokinetic characteristics, others (ceftriaxone, ceftazidime, vancomycin, *etc.*) may require other equivalent drugs [45].

The approach for the selection of oral treatment shows small differences among guidelines. The BTS guidelines recommend switching from *i.v.* third-generation cephalosporin to oral three times daily amoxicillin-clavulanate instead of oral therapy with cephalosporins (evidence level 4b evidence). As an alternative, a parenteral combination of penicillin plus levofloxacin can be switched to oral levofloxacin plus amoxicillin or oral monotherapy with levofloxacin (evidence level 4b) [2].

To highlight this, the IDSA/ATS guidelines suggest that patients who have received β-lactam macrolide combination therapy may switch to oral macrolide monotherapy, as it is a safe and cost-effective treatment in patients who do not have drug-resistant *Streptococcus pneumoniae* or Gram-negative enteric bacilli [2, 46, 47]. The antibiotics most frequently used in CAP switch strategies are shown in table 5 [48–52].

Some studies have compared different antibiotics and the benefits of the switch therapy strategy with several doses and equivalent drugs. For example, oral clarithromycin seems to be better tolerated than oral erythromycin when using macrolides [53]. With regard to cephalosporin therapy, FERNÁNDEZ *et al.* [54] compared using *i.v.* ceftriaxone for the first 3 days and then randomising patients to complete 10 days with *i.v.* ceftriaxone or oral ceftibuten (400 mg per day). There were no statistical differences between the two groups in clinical cure, radiological improvement and normalisation of the white blood cell count [54]. Recently, an oral third-generation cephalosporin (cefditoren) has been considered as a better choice when switching from previous *i.v.* third-generation cephalosporins (cefotaxime and ceftriaxone), due to its similar spectrum and better intrinsic activity [55, 56].

ATHANASSA *et al.* [57] performed a meta-analysis to evaluate the usefulness of the switch therapy in hospitalised patients with moderate-to-severe CAP. The authors found six randomised controlled trials (n=1219) whose results showed no statistical differences in an intention-to-treat analysis between early oral switch and *i.v.* treatment on several outcomes. Moreover, patients included in the early oral switch groups had lower length of hospital stay and less drug-related adverse events. These results were consistent in severe CAP patients (three studies). The final conclusion was that early switch to oral therapy may be as effective as continuous *i.v.* treatment for moderate-to-severe hospitalised CAP [57]. The main limitations were, first, that the total number of patients was not large, especially regarding severe CAP, and, secondly, that the studies were quite heterogeneous, resulting in statistical positive results but with wide confidence intervals.

Strategies and feasibility to early switch antibiotic therapy and hospital discharge

One of the main consequences of oral switch therapy is its clear beneficial impact on early hospital discharge and, therefore, it becomes an important strategy to be implemented. Once CAP patients achieve clinical stability and clinicians have switched from the *i.v.* to the oral route, there is no evidence

Table 5. Antibiotics most commonly used in ''switch'' strategies

Intravenous antibiotic	Oral antibiotic	Oral bioavailability %
Same drug/same AUC		
Levofloxacin 500 mg per 24 h	Levofloxacin 500 mg per 24 h	100
Moxifloxacin 400 mg per 24 h	Moxifloxacin 400 mg per 24 h	
Clindamycin 600–900 mg per 8 h	Clindamycin 450–600 mg per 8 h	90
Same drug/smaller AUC		
Ampicillin 1 g per 6 h	Amoxicillin 875 mg per 8 h	75–89
Amoxicillin[#] 1 g per 6 h	Amoxicillin[#] 500 mg per 8 h	
Amoxicillin-clavulanate[¶] 1–2 g per 125 mg per 8 h	Amoxicillin-clavulanate[¶] 875 mg per 125 mg per 8 h	75
Cloxacillin 1–2 g per 6 h	Cloxacillin 500 mg to 1 g per 6 h	50–75
Clarithromycin 500 mg per 12 h	Clarithromycin 500 mg per 12 h	50
Azythromycin 500 mg per 24 h	Azythromycin 500 mg per 24 h	40
Different drug/different AUC		
Ceftriaxone 1–2 g per 24 h	Cefditoren 400 mg per 12 h	

AUC: area under the curve. [#]: doses amoxicillin used in the UK [2]; [¶]: doses used in European countries are different to those used in the UK [16]. Modified from [2, 14].

of the benefits of maintaining hospital observation during oral treatment, while early hospital discharge may lead to lower nosocomial infection risk and may improve patient satisfaction. Several studies have shown the potential cost savings that an optimal earlier switch therapy and hospital discharge involves. However, a significant proportion of patients who are candidates for early switching are maintained with *i.v.* antibiotics, pointing out that this measure, demonstrated in several studies and recommended by guidelines, is still suboptimal and needs better implementation [43, 58].

Important clues for implementing early switch therapy with different strategies have been reported. MERTZ *et al.* [59] designed a before and after study evaluating the usefulness of a checklist with some criteria to indicate oral switching after 48–72 h of *i.v.* treatment. They found that the number of days with *i.v.* antibiotics was reduced by 19% without negative effects, and that fever and lack of clinical improvement were the main reasons for non-compliance [59]. Another approach is to incorporate switching criteria in clinical pathways for CAP management. CARRATALÁ *et al.* [60] proposed a three-step clinical pathway for hospitalised non-intensive care unit patients with several performance measures: early mobilisation, objective criteria for switching, and predefined discharge plan. This clinical pathway was able to reduce the median number of days of *i.v.* antibiotic (4 days in the control arm *versus* 2 days in the intervention arm) [60].

Antimicrobial stewardship programmes adapted to hospital characteristics, staff, infrastructure and size, could incorporate, among others, indications and recommendations for switching [38]. One possibility is creating specific teams, or implementing the collaboration between practitioners and pharmacists for switching therapy in the most severe cases [36]. AVDIC *et al.* [61] performed an interventional study aimed to evaluate some performance measures in CAP, specifically duration of antibiotic therapy. The intervention included educational lectures with information about duration and short-course therapy, which were combined with direct feedback with an antimicrobial stewardship team. That strategy reduced the median duration of antibiotic therapy from 10 days to 7 days, resulting in a 61% reduction of unnecessary antibiotic treatment [61].

Role of biomarkers in guiding antibiotic therapy

Definition and characteristics of biomarkers frequently used in CAP

Inflammatory biomarkers as an expression of infection and/or inflammation are useful tools in the decision-making process in CAP, both for the initiation and discontinuation of antibiotic therapy. As they provide individual information about the host response, the possibility of bacterial infection

and other physiological processes, they can be incorporated into clinical algorithms for CAP management, specifically with regard to antimicrobial duration [62]. C-reactive protein (CRP) and procalcitonin (PCT) are the most extensively studied biomarkers for monitoring the course and response of CAP. Serial measurements of CRP and PCT have demonstrated their usefulness to monitor clinical response or treatment failure at 72 h of treatment [63, 64]. Multiple interventional studies aimed to identify bacterial infection and its resolution have been performed, especially with PCT.

In this section the potential role of biomarkers, specifically PCT, in guiding duration, de-escalation and antibiotic switch therapy will be reviewed along with a summary of evidence in recent studies and in guideline recommendations.

PCT to guide duration of antibiotic therapy

Scientific-based evidence of PCT antibiotic therapy guidance

PCT is a biomarker with fast kinetics, exhibiting a rapid release and decrease in the presence of bacterial infection. The characteristic of having fast kinetics has permitted the design of studies to deciding when to initiate and to discontinue antibiotics in lower respiratory tract infections. Several studies have been conducted using serial PCT measurements to determine whether antibiotics are still needed or may be withdrawn allowing a significant reduction of antibiotic consumption without negatively impacting on clinical outcomes.

The two most important randomised controlled trials are ProCAP (Procalcitonin-guided Reduction of the duration of Antibiotic Therapy in Community-acquired Pneumonia) and ProHOSP (a multicentre, noninferiority, randomised controlled trial in hospitalised patients with low respiratory tract infections), which have compared PCT antibiotic guidance *versus* standard care of CAP [62, 65]. Recently, ProREAL, an observational and multicentre study that reflects the perspective of "real-life" PCT antibiotic guidance, was published [66]. The ProCAP and ProHOSP studies have a similar design, aimed to compare two arms of antibiotic treatment: 1) the PCT arm, with PCT measured during antibiotic treatment at days 3, 5 and 7, and with pre-established threshold serum levels for decisions (<0.25 $\mu g \cdot mL^{-1}$ discouraging antibiotics); and 2) the standard-care arm, relying on physician decisions concerning antibiotic treatment duration. Both studies showed a decrease of approximately 50% in antibiotic exposure/duration in the group treated according to PCT levels. The withdrawal of antibiotic therapy was established when PCT levels were <0.25 $\mu g \cdot mL^{-1}$ or when there was a reduction of 80–90% with respect to initial extremely high PCT levels. The ProCAP study included 302 patients and the median duration of antibiotic therapy was 5 days in the PCT arm *versus* 12 days in the standard care arm ($p<0.001$). Interestingly neither more adverse effects nor worse outcomes were found in the PCT arm [62]. In the ProHOSP study, performed in 1359 patients with lower respiratory tract infections (68% of CAP), switching to oral therapy was earlier in the PCT arm (4.1 days *versus* 4.8 days) in the whole cohort. Specifically, in the CAP group in the PCT arm, the total antibiotic duration decreased from a mean of 10.7 days to 7.2 days and the overall adverse outcome also decreased (20.2% to 16.1%). A reduction was also found in antibiotic prescription rate in the PCT arm (75.4% *versus* 87.7%) [66]. Interesting microbiological issues concerning the possible beneficial effect on avoiding nosocomial infections are not described in these studies, although the authors pointed out that overall antibiotic adverse events and outcomes are reduced.

The ProREAL study investigated the same policy concerning PCT antibiotic guidance in an observational, not randomised, study of 1759 patients (53.7% CAP). The authors corroborated a significant shortening of antibiotic treatment duration, without adverse effects [66]. In summary, the mean reduction of treatment duration in CAP was 3.3 days, which was also found in a meta-analysis [67].

In severe intensive care unit cases, the studies of PCT antibiotic guidance are scarce. The ProRATA multicentre study (Procalcitonin to Reduce Antibiotic Treatments in Acutely Ill Patients) was performed in France in a non-surgical intensive care unit. The study was specifically designed to evaluate if PCT antibiotic guidance was superior for reducing antibiotic exposure using predefined

PCT levels. The authors found a significant reduction of antibiotic treatment from 14.3 days to 11.6 days, with non-inferiority in death outcomes. One important limitation was that the PCT algorithm was finally applied in only 53% of the patients [68].

A major consideration when using a new diagnostic test is the cost associated with the test with respect to the potential for producing a cost saving. One meta-analysis concluded that PCT in the critical care setting may be cost effective because of the high antibiotic costs in critically ill patients [69]. Although the same may not necessarily be true for general hospital inpatients with less expensive antibiotics, secondary costs due to side-effects and the emergence of antibiotic resistance should be considered. To date, there are no cost-effectiveness studies of PCT antibiotic guidelines. Future intervention studies should propose PCT protocols with specific cut-offs and evaluate their impact on patient-relevant outcomes. The evidence suggests that using PCT can lead to better use of antibiotics and de-escalation, without safety concerns while improving costs [70].

Guideline recommendations: biomarkers usefulness in guiding antibiotic therapy

The incorporation of biomarkers in CAP guideline recommendations is scarce; nil for antibiotic initiation or choice and rather small for monitoring clinical response and/or discontinuing therapy. The BTS [2] and ERS [3] guidelines suggested that CRP may have a significant potential to improve severity assessment; however, this has not been sufficiently evaluated to allow the decision to be taken to hospitals, and there is a lack of information about biomarkers usefulness for antibiotic guidance. However, the ERS guidelines [3] recommend that CRP should be remeasured and a new chest radiograph must be obtained for evaluation of patients not responding after 3 days of treatment.

In the ERS guidelines, WOODHEAD *et al.* [3] broaden the potential usefulness of biomarkers. The authors suggested that PCT may be useful in guiding treatment duration [3, 62, 65, 71]. It may even be useful in the most severe cases (sepsis and septic shock) [68, 72].

Although different CAP management guidelines do not have specific recommendations about biomarkers' antibiotic guidance yet (except the ERS guidelines [3]), recent well-structured randomised trials such as the ProCAP, ProHOSP and ProREAL studies have demonstrated the usefulness of PCT for that task. The implementation of this new PCT antibiotic guidance algorithm may lead clinicians to improve antibiotic use, shorten the duration course and decide on an early switch to oral therapy in the daily clinical practice, which might reduce antibiotic resistance and adverse events.

Conclusion

To conclude, the latest guideline recommendations on duration, route and switch therapy are being updated with results of several trials and meta-analyses. Available data suggest that an appropriate antibiotic class selection (spectrum and pharmacokinetic/pharmacodynamics) associated with proper course monitoring in CAP patients may shorten antibiotic regimens to 5–7 days, reducing the chance for adverse events or microorganism resistance. Moreover, in the past decade, different authors have proposed the use of PCT algorithms to reduce the antibiotic treatment duration, although there is not enough evidence to apply this in the switching therapy strategy. New clinical trials are needed to strengthen the scientific evidence and to improve adherence to CAP management guidelines in daily clinical practice.

Statement of Interest

None declared.

References

1. Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44: Suppl. 2, S27–S72.

2. Lim WS, Baudouin SV, George RC, *et al.* BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; 64: Suppl. 3, iii1–iii55.
3. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections. *Clin Microbiol Infect* 2011; 17: Suppl. 6, E1–E59.
4. Menéndez R, Torres A, Reyes S, *et al.* Compliance with guidelines-recommended processes in pneumonia: impact of health status and initial signs. *PLoS One* 2012; 7: e37570.
5. Dean NC, Bateman KA, Donnelly SM, *et al.* Improved clinical outcomes with utilization of community-acquired pneumonia guideline. *Chest* 2006; 130: 794–799.
6. Chan R, Hemeryck L, O'Regan M, *et al.* Oral *versus* intravenous antibiotics for community acquired lower respiratory tract infection in general hospital: open randomized controlled trial. *BMJ* 1995; 310: 1360–1362.
7. MacGregor RR, Grazianj AL. Oral administration of antibiotics: a rational alternative to the parenteral route. *Clin Infect Dis* 1997; 24: 457–467.
8. Woodhead M, Welch CA, Harrison DA, *et al.* Community-acquired pneumonia on the intensive care unit: secondary analysis of 17,869 cases in the ICNARC Case Mix Programme Database. *Crit Care* 2006; 10: Suppl. 2, S1.
9. Di Maria G, Spicuzza L, Polosa R. Antibiotics and new guidelines for the treatment of lower respiratory tract infections. *In:* Cazzola M, Blasi F, Ewig S, eds. Antibiotics and the Lung. *Eur Respir Monogr* 2004; 28: 175–188.
10. Bauer MP, Kuijper EJ, Van Dissel JT. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for *Clostridium difficile* infection (CDI). *Clin Microbiol Infect* 2009; 15: 1067–1079.
11. Aliberti S, Blasi F, Zanaboni AM, *et al.* Duration of antibiotic therapy in hospitalized patients with community-acquired pneumonia. *Eur Respir J* 2010; 36: 128–134.
12. Contopoulos-Ioannidis DG, Ioannidis JP, Chew P, *et al.* Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for lower respiratory tract infections. *J Antimicrob Chemother* 2001; 48: 691–703.
13. Foulds G, Shepard RM, Johnson RB. The pharmacokinetics of azithromycin in human serum and tissues. *J Antimicrob Chemother* 1990; 25: 73–82.
14. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; 26: 1138–1180.
15. Niederman M. Cost-effective antibiotic management of community acquired pneumonia. *In:* Cazzola M, Blasi F, Ewig S, eds. Antibiotics and the Lung. *Eur Respir Monogr* 2004; 28: 198–210.
16. Torres A, Barberán J, Falguera M, *et al.* Guía multidisciplinar para la valoración pronóstica, diagnóstico y tratamiento de la neumonía adquirida en la comunidad [Multidisciplinary guidelines for the management of community-acquired pneumonia]. *Med Clin (Barc)* 2013; 140: 223.e1–223.e19.
17. Scalera NM, File TM Jr. Determining the duration of therapy for patients with community-acquired pneumonia. *Curr Infect Dis Rep* 2013; 15: 191–195.
18. File TM Jr. Clinical efficacy of newer agents in short-duration therapy for community-acquired pneumonia. *Clin Infect Dis* 2004; 39: Suppl. 3, S159–S164.
19. Schrag SJ, Peña C, Fernández J, *et al.* Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial. *JAMA* 2001; 286: 49–56.
20. Lode H. Safety and tolerability of commonly prescribed oral antibiotics for the treatment of respiratory tract infections. *Am J Med* 2010; 123: Suppl. 4, S26–S38.
21. Kardas P. Patient compliance with antibiotic treatment for respiratory tract infections. *J Antimicrob Chemother* 2002; 49: 897–903.
22. Reyes H, Guiscafré H, Muñoz O, *et al.* Antibiotic noncompliance and waste in upper respiratory infections and acute diarrea. *J Clin Epidemiol* 1997; 50: 1297–1304.
23. Hayashi Y, Paterson DL. Strategies for reduction in duration of antibiotic use in hospitalized patients. *Clin Infect Dis* 2011; 52: 1232–1240.
24. Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, *et al.* Short- *versus* long-course antibacterial therapy for community-acquired pneumonia: a meta-analysis. *Drugs* 2008; 68: 1841–1854.
25. Li JZ, Winston LG, Moore DH, *et al.* Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. *Am J Med* 2007; 120: 783–790.
26. Dunbar LM, Wunderink RG, Habib MP, *et al.* High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. *Clin Infect Dis* 2003; 37: 752–760.
27. Dunbar LM, Khashab MM, Kahn JB, *et al.* Efficacy of 750-mg, 5-day levofloxacin in the treatment of community-acquired pneumonia caused by atypical pathogens. *Curr Med Res Opin* 2004; 20: 555–563.
28. Tellier G, Niederman MS, Nusrat R, *et al.* Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. *J Antimicrob Chemother* 2004; 54: 515–523.
29. File TM Jr, Mandell LA, Tillotson G, *et al.* Gemifloxacin once daily for 5 days *versus* 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double blind study. *J Antimicrob Chemother* 2007; 60: 112–120.
30. Leophonte P, Choutet P, Gaillat J, *et al.* Efficacy of ten day course of ceftriaxone compared to a shortened five day course in the treatment of community-acquired pneumonia in hospitalized adults with risk factors. *Med Mal Infect* 2002; 32: 369–381.

31. El Moussaoui R, de Borgie CA, van den Broek P, *et al.* Effectiveness of discontinuing antibiotic treatment after three days *versus* eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. *BMJ* 2006; 332: 1355.
32. Choudhury G, Mandal P, Singanayagam A, *et al.* Seven-day antibiotic courses have similar efficacy to prolonged courses in severe community-acquired pneumonia – a propensity-adjusted analysis. *Clin Microbiol Infect* 2011; 17: 1852–1858.
33. Aguado JM, Fortún J, eds. Guía de recomendaciones en la Terapia Secuencial Antibiótica (TSA) [Guideline recommendations in sequential antibiotic therapy]. Madrid, Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica, 2006. www.seimc.org/contenidos/documentoscientificos/guiasclinicas/seimc-GuiaClinica3_2006_TSA.pdf
34. Parker SE, Davey PG. Pharmacoeconomics of intravenous drug administration. *Pharmacoeconomics* 1992; 1: 103–115.
35. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. *Arch Intern Med* 2001; 161: 1837–1842.
36. Falguera M, Ruiz-González A, Schoenenberger JA, *et al.* Prospective, randomized study to compare empirical treatment *versus* targeted treatment on the basis of the urine antigen results in hospitalised patients with community-acquired pneumonia. *Thorax* 2010; 65: 101–106.
37. Septimus EJ, Owens RC Jr. Need and potential of antimicrobial stewardship in community hospitals. *Clin Infect Dis* 2011; 53: Suppl. 1, S8–S14.
38. Niederman MS. The importance of de-escalating antimicrobial therapy in patients with ventilator-associated pneumonia. *Semin Respir Crit Care Med* 2006; 27: 45–50.
39. Ramírez JA, Srinath L, Ahkee S, *et al.* Early switch from intravenous to oral cephalosporins in the treatment of hospitalized patients with community-acquired pneumonia. *Arch Intern Med* 1995; 155: 1273–1276.
40. Mandell LA, Bergeron MG, Gribble MJ, *et al.* Sequential antibiotic therapy: effective cost management and patient and patient care. *Can J Infect Dis* 1995; 6: 306–315.
41. Ramirez JA, Vargas S, Ritter GW, *et al.* Early switch from intravenous to oral antibiotics and early hospital discharge: a prospective observational study of 200 consecutive patients with community-acquired pneumonia. *Arch Intern Med* 1999; 159: 2449–2454.
42. Oosterheert JJ, Bonten MJ, Schneider MM, *et al.* Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. *BMJ* 2006; 333: 1193.
43. Engel MF, Postma DF, Hulscher ME, *et al.* Barriers to an early switch from intravenous to oral antibiotic therapy in hospitalized patients with CAP. *Eur Respir J* 2013; 41: 123–130.
44. Castro-Guardiola A, Viejo-Rodríguez AL, Soler-Simons S, *et al.* Efficacy and safety of oral and early-switch therapy for community-acquired pneumonia: a randomized controlled trial. *Am J Med* 2001; 111: 367–374.
45. Cairns C. Implementation of sequential therapy programmes – a pharmacist's view. *J Infect* 1998; 37: Suppl. 1, 55–59.
46. Paladino JA, Gudgel LD, Forrest A, *et al.* Cost-effectiveness of IV-to-oral switch therapy: azithromycin *vs* cefuroxime with or without erythromycin for the treatment of community-acquired pneumonia. *Chest* 2002; 122: 1271–1279.
47. Zervos M, Mandell LA, Vrooman PS, *et al.* Comparative efficacies and tolerabilities of intravenous azithromycin plus ceftriaxone and intravenous levofloxacin with step-down oral therapy for hospitalized patients with moderate to severe community-acquired pneumonia. *Treat Respir Med* 2004; 3: 329–336.
48. Hunter KA, Dormaier GK. Pharmacist managed intravenous to oral step-down program. *Clin Ther* 1995; 17: 534–540.
49. MacGowan AP, Bowker KE. Sequential antimicrobial therapy: pharmacokinetic and pharmacodynamic considerations in sequential therapy. *J Infect* 1998; 37: Suppl. 1, 30–36.
50. Frighetto L, Nickoloff D, Martinusen SM, *et al.* Intravenous-to-oral stepdown program: four years of experience in a large teaching hospital. *Ann Pharmacother* 1992; 26: 1447–1451.
51. Janknegt R, Van der Meer JWM. Sequential therapy with intravenous and oral cephalosporins. *J Antimicrob Chemother* 1994; 33: 169–177.
52. Zamin MT, Pitre MM, Conly JM. Development of an intravenous-to oral route conversion program for antimicrobial therapy at a Canadian tertiary care health facility. *Ann Pharmacother* 1997; 31: 564–570.
53. Anderson G, Esmonde TS, Coles S, *et al.* A comparative safety and efficacy study of clarithromycin and erythromycin stearate in community-acquired pneumonia. *J Antimicrob Chemother* 1991; 27: 117–124.
54. Fernández P, San Martín L. Neumonia adquirida en la comunidad: terapia secuencial de cefalosporina intravenosa a cefalosporina oral [Community acquired pneumonia: from intravenous to oral cephalosporin sequential therapy]. *Rev Med Chil* 2000; 128: 267–272.
55. Barberán J, Mensa J. Cefditoren en las infecciones de vias respiratorias bajas adquiridas en la comunidad [Cefditoren and community-acquired lower respiratory tract infections (corrected)]. *Rev Esp Quimioter* 2009; 22: 144–150.
56. Giménez MJ, Gómez-Lus ML, Valdés L, *et al.* Situación de la cefalosporina oral de tercera generación cefditoreno pivoxil en el tratamiento de la infección comunitaria del adulto [The role of the third-generation oral cephalosporin cefditoren pivoxil in the treatment of community-acquired infection in adults]. *Rev Esp Quimioter* 2005; 18: 210–216.

57. Athanassa Z, Makris G, Dimopoulos G, *et al.* Early switch to oral treatment in patients with moderate to severe community-acquired pneumonia: a meta-analysis. *Drugs* 2008; 68: 2469–2481.
58. Ramirez JA. Clinical stability and switch therapy in hospitalised patients with community-acquired pneumonia: are we there yet? *Eur Respir J* 2013; 41: 5–6.
59. Mertz D, Koller M, Haller P, *et al.* Outcomes of early switching from intravenous to oral antibiotics on medical wards. *J Antimicrob Chemother* 2009; 64: 188–199.
60. Carratalá J, García-Vidal C, Ortega L, *et al.* Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in community-acquired pneumonia: a randomized controlled trial. *Arch Intern Med* 2012; 172: 922–928.
61. Avdic E, Cushinotto LA, Hughes AH, *et al.* Impact of an antimicrobial stewardship intervention on shortening the duration of therapy for community-acquired pneumonia. *Clin Infect Dis* 2012; 54: 1581–1587.
62. Christ-Crain M, Stolz D, Bingisser R, *et al.* Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2006; 174: 84–93.
63. Menéndez R, Martínez R, Reyes S, *et al.* Stability in community-acquired pneumonia: one step forward with markers? *Thorax* 2009; 64: 987–992.
64. Kolditz M, Ewig S, Höffken G. Management-based risk prediction in community acquired pneumonia by scores and biomarkers. *Eur Respir J* 2013; 41: 974–984.
65. Schuetz P, Christ-Crain M, Thomann R, *et al.* Effect of procalcitonin-based guidelines *vs* standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* 2009; 309: 1059–1066.
66. Albrich WC, Dusemund F, Bucher B, *et al.* Effectiveness and safety of procalcitonin-guided antibiotic therapy in lower respiratory tract infection in "real life": an international, multicenter poststudy survey (ProREAL). *Arch Intern Med* 2012; 172: 715–722.
67. Schuetz P, Briel M, Christ-Crain M, *et al.* Procalcitonin to guide imitation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. *Clin Infect Dis* 2012; 55: 651–662.
68. Bouadma L, Luyt CE, Tubach F, *et al.* Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010; 375: 463–474.
69. Heyland DK, Johnson AP, Reynolds SC, *et al.* Procalcitonin for reduced antibiotic exposure in the critical care setting: a systematic review and an economic evaluation. *Crit Care Med* 2011; 39: 1792–1799.
70. Schuetz P, Amin DN, Greenwald JL. Role of procalcitonin in managing adult patients with respiratory tract infections. *Chest* 2012; 141: 1063–1073.
71. Kristoffersen KB, Søgaard OS, Wejse C, *et al.* Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission – a randomized trial. *Clin Microbiol Infect* 2009; 15: 481–487.
72. Nobre V, Harbarth S, Graf JD, *et al.* Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med* 2008; 177: 498–505.

Chapter 13

Acute respiratory failure due to CAP

Miquel Ferrer

SUMMARY: Patients with severe community-acquired pneumonia (CAP) often present acute respiratory failure (ARF). In less severe cases, oxygen therapy titrated to achieve acceptable arterial oxygenation is indicated.

Noninvasive ventilation (NIV) is often indicated in patients with CAP and severe ARF. The populations of patients with CAP with better response to NIV are those with previous cardiac or respiratory disease. Thus, the use of NIV in patients with CAP without these pre-existing diseases should be very cautious and under strict monitoring conditions due to high rates of treatment failure. Unnecessary delay in intubation of patients who fail treatment with NIV seems to be associated with mortality.

Continuous positive airway pressure (CPAP) has been used to treat ARF in several conditions characterised by alveolar collapse. However, the efficacy in pneumonia seems to be limited to immunosuppressed patients with pulmonary complications. The helmet is a promising new interface for the use of NIV or CPAP, particularly in hypoxaemic nonhypercapnic patients.

Invasive mechanical ventilation is indicated in patients with life-threatening ARF or in those who have failed NIV treatment.

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Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality [1, 2]. Conceptually, severe CAP is pneumonia with severe acute respiratory failure (ARF), severe sepsis or organ system dysfunction, or carrying a high risk of death [2–4].

Direct admission to an intensive care unit (ICU) is required for patients with septic shock or ARF requiring invasive mechanical ventilation (IMV), defined as major severity criteria in the current Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines used to define severe CAP [1]. Admission to an ICU is also recommended for patients with other minor severity criteria (table 1). The IDSA/ATS guidelines recommended that patients with three or more minor severity criteria, in the absence of major criteria, be admitted to an ICU. Among all criteria that define severe CAP, the need for IMV, severe arterial hypoxaemia and increased respiratory rate are related to ARF.

ARF in patients with CAP can be suspected when several symptoms and signs are present, such as dyspnoea, tachypnoea, cyanosis, nasal flaring, decreased consciousness, intercostal retraction, use

of accessory muscles or thoracic-abdominal paradoxical motion. As in the general population, ARF is defined by an arterial oxygen tension (P_{aO_2}) <60 mmHg at rest, breathing room air at sea level, and/or arterial carbon dioxide tension (P_{aCO_2}) >50 mmHg.

Table 1. Criteria for severe community-acquired pneumonia according to the Infectious Diseases Society of America/American Thoracic Society guidelines

Minor criteria
Respiratory rate[#] $\geq$30 breaths·min^{-1}
P_{aO_2}/F_{IO_2} $\leq$250[#]
Multilobar infiltrates
Confusion/disorientation
Uraemia (BUN level $\geq$20 mg·dL^{-1})
Leukopenia (WBC count $<4\times10^9$ cells·L^{-1})
Thrombocytopenia (platelet count $<100\times10^9$ cells·L^{-1})
Hypothermia (core temperature <36°C)
Hypotension requiring aggressive fluid resuscitation
Major criteria
Invasive mechanical ventilation
Septic shock with the need for vasopressors

P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; BUN: blood urea nitrogen; WBC: white blood cells. [#]: the need for noninvasive ventilation can substitute for respiratory rate $\geq$30 breaths·min^{-1} or P_{aO_2}/F_{IO_2} $\leq$250. Reproduced from [1], with permission from the publisher.

Pulmonary gas exchange is often altered in patients with pneumonia. Human studies have shown that the predominant mechanism of hypoxaemia in bacterial pneumonia is the presence of both intrapulmonary shunt and mild-to-moderate ventilation/perfusion (V'/Q') mismatching [5–7]. Both experimental and clinical studies in pneumonia have pointed out that increased shunt and V'/Q' inequalities could be related to partial ablation of hypoxic pulmonary vasoconstriction [5, 8, 9].

Assessment of severity

The severity of hypoxaemia is considered to be one of the prognostic factors of patients with bacterial pneumonia [10]. In the assessment of severity of ARF, parameters such as respiratory rate, P_{aO_2}, oxygen saturation or the ratio of P_{aO_2} to inspiratory oxygen fraction (F_{IO_2}) may be useful when taking decisions such as supporting treatment or patient allocation [4].

Monitoring of patients is strongly advised in the presence of: 1) clinical criteria, such as dyspnoea at rest, inability to pronounce phrases or words, decreased consciousness, respiratory rate above 30 breaths·min^{-1}, central cyanosis, intercostal retraction, use of accessory muscles or thoracic-abdominal paradoxical motion; or 2) blood gas parameters, such as persistence of arterial hypoxaemia (P_{aO_2} <60 mmHg) despite high levels of F_{IO_2}, or hypercapnia (P_{aCO_2} >50 mmHg) with respiratory acidosis (arterial pH <7.35).

Supporting treatment for ARF

The cornerstone in the treatment of pneumonia is antibiotic therapy. Patients with signs of ARF may receive oxygen supplementation or/and ventilator support. Ventilator support is often indicated in patients with CAP and severe ARF [11]. Noninvasive ventilation (NIV) has been used in these patients in order to overcome an episode of severe ARF without the need for endotracheal intubation and IMV [12]. However, in the most severe cases, such as those with life-threatening ARF, IMV will be required. The objective of all the supporting measures for ARF is to gain time for the antibiotic treatment to cure the pneumonia. This chapter will revise the currently available information on the supportive treatment of ARF in patients with CAP.

Oxygen therapy

Oxygen therapy is indicated in less severe cases of ARF. The main purpose of oxygen therapy is keeping levels of P_{aO_2} appropriate, in order to achieve arterial oxygen saturation >90–92%, which usually requires P_{aO_2} >60–65 mmHg. Patients with predominant intrapulmonary shunt as the

mechanism of abnormal gas exchange are expected to respond poorly in terms of oxygenation to increases in F_{IO_2}. In contrast, this response is expected to be better when V'/Q' mismatch is the predominant mechanism of abnormal gas exchange. As patients with pneumonia share both mechanisms, the response to increased F_{IO_2} may be variable.

The choice of F_{IO_2} may depend on the characteristics of respiratory failure. In cases of hypercapnic respiratory failure, slightly elevated F_{IO_2} is recommended. Otherwise, the central hypoxic stimulus can be inhibited and pulmonary vasoconstriction can be released, potentially resulting in worsening hypercapnia and respiratory acidosis. This is particularly relevant in patients who are hypercapnic or at risk of hypercapnia, such as those with chronic obstructive pulmonary disease (COPD), hypoventilation syndromes or neuromuscolar disease. Although high levels of F_{IO_2} are generally considered safe in cases of hypoxaemic respiratory failure, recent data in patients presenting with suspected CAP without COPD or hypercapnia showed that high-concentration oxygen therapy increases the levels of P_{aCO_2} compared with titrated oxygen [13]. This suggests that the potential increase in P_{aCO_2} with high-concentration oxygen therapy is not limited to COPD, but may also occur in other respiratory disorders with abnormal gas exchange.

Noninvasive ventilation

Based on controlled clinical trials, NIV is now considered a first-line ventilatory treatment in selected patients with severe exacerbation of COPD and hypercapnic respiratory failure [14] and acute cardiogenic pulmonary oedema (CPO) [15]. The benefits of NIV appear to be the consequence of avoiding tracheal intubation and IMV and the associated morbidity and mortality. Morbidities include an increased risk of ventilator-associated pneumonia [16], ventilator-induced lung injury [17], the increased requirement for sedation that contributes to prolonged ventilation, and complications of the upper airway related to prolonged translaryngeal intubation.

However, the role of NIV in other types of patients is still under debate. It is possible that other populations at risk of complications related to IMV may benefit from the use of NIV. However, the efficacy of NIV in patients with different types of hypoxaemic ARF is less evident from controlled clinical trials. Although patients with hypoxaemic ARF were less likely to require tracheal intubation when NIV was added to standard therapy, a systematic review of the literature did not support the routine use of NIV in all patients with hypoxaemic ARF, due to a less clear effect on mortality and the heterogeneity found among studies, suggesting that effectiveness varies among different populations [18].

The first problem in addressing patients with hypoxaemic ARF is the heterogeneity of this condition. Studies assessing the outcome of patients with hypoxaemic ARF treated with NIV in the ICU identified up to nine different groups of patients, with substantial differences in outcomes among them [19]. Moreover, a majority of clinical trials that assessed the efficacy of NIV in patients with hypoxaemic ARF studied mixed populations of patients, with controversial results when all these trials are analysed together. In contrast, few studies have specifically assessed the usefulness of NIV in patients with pneumonia [20] and it is even considered controversial due to a major variability in failure rates [20–23], which are generally higher than those observed in COPD [14] or acute CPO [15].

Studies on NIV often include pneumonia in the heterogeneous condition of hypoxaemic ARF, which was independently associated with NIV failure in a multicentre study [24]. However, large published series of hospitalised patients with CAP report high rates of chronic respiratory or cardiac comorbidities [25, 26]. Hence, a recent report on patients with CAP treated with NIV in the ICU reported a substantial proportion of patients with previous cardiac or respiratory disease, resulting in a high proportion of hypercapnic respiratory failure among them [27]. Thus, the outcome of NIV in patients with CAP from studies that have excluded COPD or hypercapnic patients [19, 21, 22, 28] should not be extrapolated to general CAP populations treated with NIV.

NIV and outcome of patients with pneumonia

Pneumonia in patients treated with NIV is persistently associated with poor outcome in the literature. The first study that found this association was a retrospective analysis of 59 episodes of ARF in 47 patients with COPD exacerbations. In 46 of these episodes, NIV was effective, and in 13 it failed and the patients needed tracheal intubation and IMV [29]. Among other findings, a univariate analysis assessing predictors of NIV failure found pneumonia to be the cause of exacerbation associated with higher failure of NIV. In this study, pneumonia was the cause of 38% of unsuccessful episodes and 9% of successful episodes of ARF. While the failure rate of patients with other causes of exacerbation was 16%, the failure rate of patients with pneumonia was 56%.

A multinational study in eight ICUs analysed the evolution of 356 patients who received NIV for an episode of severe hypoxaemic ARF in relation with the aetiology of the episode [19]. Among the different causes of hypoxaemic ARF, the highest rates of tracheal intubation corresponded to patients with acute respiratory distress syndrome (ARDS) (70%) and CAP (60%). A multivariate analysis of predictors of NIV failure found the presence of ARDS or CAP a significant and independent predictor of NIV failure, with an adjusted odds ratio of 3.75. Other independent predictors of NIV failure were age >40 years, higher scores of severity at ICU admission and worse hypoxaemia after 1 h of NIV treatment.

Another prospective study analysed 24 patients without underlying chronic respiratory disease who were treated with NIV because of severe CAP and ARF [21]. In general, the use of NIV was followed by a decrease in respiratory rate and increase in arterial hypoxaemia after 30 min, with return to the baseline values after NIV was removed. However, the overall intubation rate was 67% in these patients. Among others, advanced age and lower levels of arterial oxygenation were predictors for intubation. Intubation was associated with higher mortality and longer length of hospital stay. In contrast, those patients in whom NIV avoided intubation had a very favourable outcome. Due to the good outcome in these patients when tracheal intubation was avoided and the fact that the assessment of the efficacy of NIV resulted in minimal delay in intubation, the authors of this study suggested that these patients could undergo a trial of NIV with appropriate monitoring in order to avoid unnecessary delay in intubation.

This conflict between a favourable physiological response to NIV and a poor clinical evolution of patients with severe CAP was observed in another study in patients with severe hypoxaemic ARF, 18 with severe CAP and 15 with CPO [22]. Both groups had similar baseline levels of arterial hypoxaemia, respiratory rate and heart rate. The improvement in arterial hypoxaemia and heart rate was similar in both groups of patients, while respiratory frequency improved only in patients with CPO when NIV was applied. The intubation rate was higher and the hospital length of stay was longer in patients with pneumonia. As expected, the hospital mortality rate was substantially higher in intubated than in non-intubated patients.

In the light of these results, we can conclude that, in patients with severe hypoxaemic ARF who need NIV, those whose cause of respiratory failure is pneumonia are among those with worse outcome, even with similar levels of arterial hypoxaemia. However, prospective randomised clinical trials are needed in order to assess whether NIV is effective in patients with severe CAP.

NIV in CAP

Few controlled trials have assessed the efficacy of NIV in patients with severe pneumonia. The only prospective randomised clinical trial in patients with severe CAP included 56 patients who were allocated to receive conventional treatment with or without NIV [20]. This study demonstrated that patients who had received NIV together with conventional treatment had a lower rate of tracheal intubation (21% *versus* 50%, $p<0.03$) and a shorter stay in the intermediate care unit than those who received conventional treatment only, although the length of hospital stay and hospital mortality were similar between both groups. This study also showed, in a subset analysis,

that the significant benefits of NIV occurred in patients with COPD and hypercapnic respiratory failure only; this subset of patients had also a lower mortality after 2 months (11% *versus* 63%, p=0.05). In contrast, patients with neither COPD nor hypercapnic respiratory failure did not benefit from NIV. Although these results were promising, the routine use of NIV in patients with CAP and without COPD has not been clearly established. Similarly, a recent prospective study on patients with CAP and severe ARF treated with NIV in the ICU showed a higher success rate of NIV in those patients with previous cardiac or respiratory disease as compared with those with *de novo* ARF [27].

A more recent prospective randomised clinical trial in patients with severe hypoxaemic ARF demonstrated that NIV decreased the need for tracheal intubation and decreased ICU mortality, compared with high-concentration oxygen therapy [23]. Moreover, a subgroup analysis observed that patients with pneumonia as the cause of the episode of hypoxaemic ARF were those in whom NIV showed significant benefits; in this subset of patients, the benefits in decreasing tracheal intubation and ICU mortality remained. With regard to the other subsets of patients, there was a nonsignificant trend to a lower rate of NIV failure in patients with thoracic trauma, and NIV failure rates in patients from this study with CPO and ARDS were very low and high, respectively, without differences between patients treated with NIV and those from the control group [23]. In this study, the use of NIV resulted in a faster improvement of arterial hypoxaemia and tachypnoea, compared with high-concentration oxygen therapy (fig. 1). NIV was also associated with a lower rate of septic shock and a trend to a lower incidence of hospital-acquired pneumonia.

Concerns have been raised due to the high mortality rate of patients who fail NIV treatment, particularly in those with hypoxaemic ARF and without previous cardiac or respiratory disease (*de novo* ARF), and the possibility that unnecessary delay of intubation results in excess mortality [24, 30]. In particular, an actual mortality of patients intubated after NIV failure higher than mortality predicted by severity scores has been reported [30]. However, these comparisons may be misleading, since severity scores often underestimate hospital mortality in ICU patients [31, 32]. A recent report on the use of NIV in patients with CAP and severe ARF found for the first time a consistent association between delayed intubation and increased mortality in patients with CAP and *de novo* ARF (fig. 2) [27]. Longer duration of NIV before intubation was not related to severity of patients at admission in this study. Moreover, patients with shock who needed intubation failed NIV earlier than those without shock. Therefore, this excess of mortality was attributed by the authors to delayed intubation rather than a more severely ill selected population. In contrast, no relationship was found between delayed intubation and mortality in patients with CAP and previous cardiac or respiratory disease from this study [27].

Recently, the usefulness and success of NIV were assessed in a prospective, observational cohort of 177 patients with influenza A (H1N1) virus pneumonia admitted to ICUs [33]. Clinicians used NIV in 26% of patients, and treatment was effective in 41% of them. NIV success was associated with shorter hospital stay and mortality was similar to nonventilated patients, while NIV failure was associated with mortality similar to those who were intubated from the start.

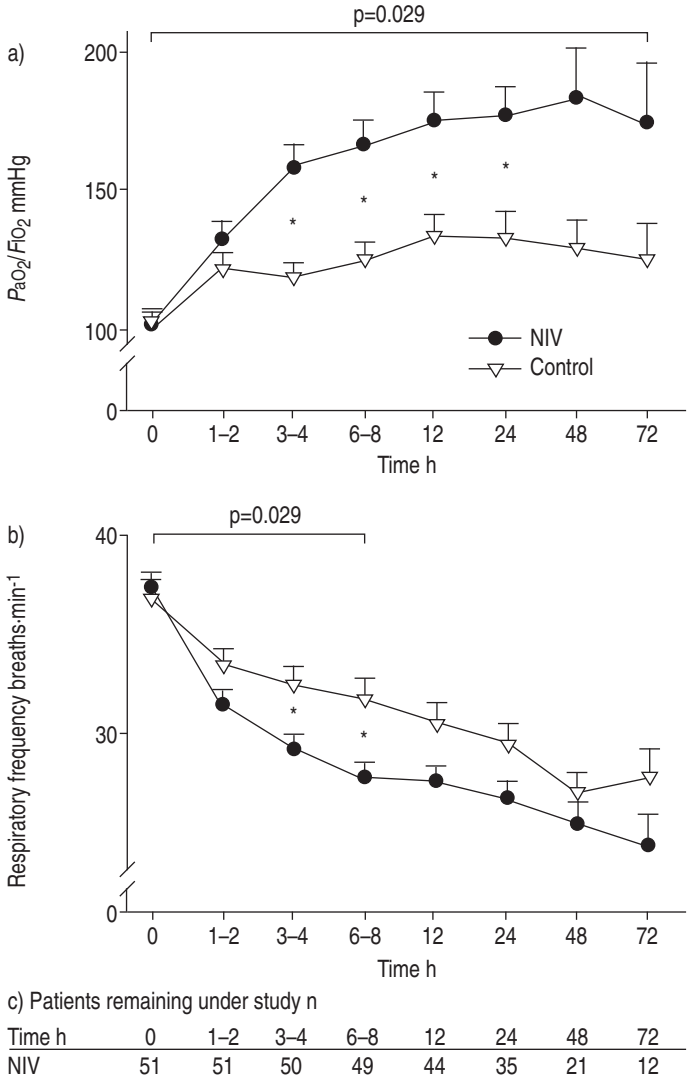
In summary, patients with severe CAP who receive NIV as a support for severe hypoxaemic ARF are among those with the highest rate of NIV failure. For this reason, when NIV is indicated in these patients, they should be managed in a setting with appropriate staff and equipment resources for correct monitoring, in order to detect evidence of NIV failure early and avoid unnecessary delay in the intubation of patients. However, an appropriate selection of patients with severe CAP and the addition of NIV to the standard treatment may decrease the likelihood of needing intubation.

NIV in immunosuppressed patients with pulmonary complications

The early application of NIV may be extremely helpful in immunosuppressed patients with pulmonary infiltrates and ARF, in whom intubation dramatically increases the risk of pneumonia, infections and ICU mortality.

The efficacy of NIV was analysed retrospectively in 35 patients with hypoxaemic ARF after stem cell transplantation who were directly ventilated in the bone marrow transplant unit [34]. NIV was delivered by a standard face mask or helmet. Out of the 82 patients who developed respiratory failure, 47 patients were initially intubated and mechanically ventilated. None of them survived. 35 patients initially underwent NIV. Seven (20%) of them survived and were discharged from the hospital. The authors concluded that, in patients with ARF after stem cell transplantation, NIV could improve prognosis when compared to a group of patients who constantly die if they receive mechanical ventilation.

Two trials evaluated NIV, as opposed to standard treatment alone, in immunosuppressed patients characterised by a respiratory rate >30 breaths·min^{-1} and PaO_2/FIO_2 <200 mmHg. ANTONELLI *et al.* [35] compared NIV with standard therapy in solid organ transplant recipients with hypoxaemic ARF. Within the first hour of treatment, PaO_2/FIO_2 improved in 70% of patients in the NIV group and in only 25% of patients receiving medical therapy alone. NIV was associated with a significant reduction in the rate of intubation, complications, mortality and duration of ICU stay among survivors. In patients with immunosuppression secondary to haematological malignancies, transplantation or HIV infection, HILBERT *et al.* [36] compared early NIV with standard treatment. All patients had fever, bilateral pulmonary infiltrates and hypoxaemia. Fewer patients in the NIV group required intubation, had serious complications or died in the ICU or in the hospital. It has been shown that NIV, especially when applied early, can significantly ameliorate the conditions of these patients, reduce need for intubation and overall mortality.



c) Patients remaining under study n

Time h	0	1–2	3–4	6–8	12	24	48	72
NIV	51	51	50	49	44	35	21	12
Control	54	54	52	49	44	38	20	15

Figure 1. Time-course evolution (mean±SEM) of arterial hypoxaemia, as assessed by a) the ratio of arterial oxygen tension (PaO^2) to inspiratory oxygen fraction (FIO^2) and b) respiratory frequency, in patients treated with noninvasive ventilation (NIV) and controls. Both variables improved with time in the two groups. *: $p<0.05$, classed as significant differences between the two groups at individual time-points; after Bonferroni correction, the improvement of the two variables was significantly greater in the NIV group 3–4 h after randomisation, and remained significantly greater 24 and 6–8 h after randomisation for PaO^2/FIO^2 ratio and respiratory frequency, respectively. c) The number of patients remaining under study at each time-point in the two groups. The time-course decrease of patients corresponds to those meeting criteria to terminate the protocol. Reproduced from [23] with permission from the publisher.

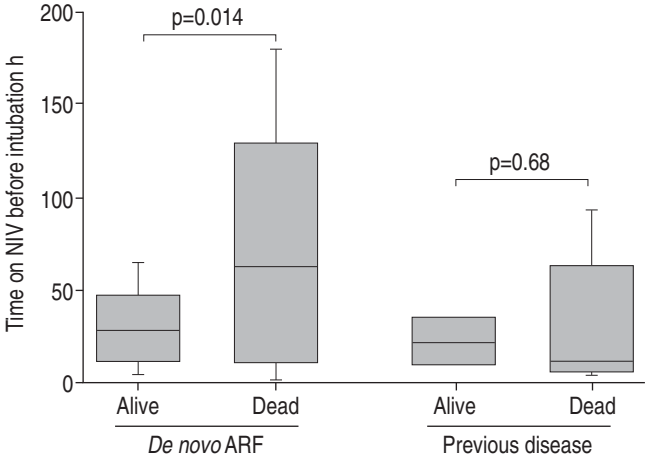


Figure 2. Duration of noninvasive ventilation (NIV) in patients who needed intubation and survived or died in the hospital. Patients studied had either *de novo* acute respiratory failure (ARF) or previous cardiac or respiratory disease. The upper and lower limits of the boxes represent the interquartile range, the inner horizontal line represents the median value, and the upper and lower vertical lines represent percentiles 5 and 95, respectively, of survivors and nonsurvivors for intubated patients from each group. Data from [27].

Continuous positive airway pressure

Effects of continuous positive airway pressure on the respiratory system

Continuous positive airway pressure (CPAP) has been used to treat ARF in several conditions. Collapsed, nonventilated alveoli represent a common example of intrathoracic shunt causing hypoxaemia that typically does not respond to oxygen administration. In this case, the only way to improve gas exchange is alveolar recruitment induced by CPAP. Patients breathe against a constant resistance to a supra-atmospheric pressure. This increase of airway pressure is present during the whole breathing cycle; in particular, positive end-expiratory pressure (PEEP) allows the collapsed alveoli to remain open also during expiration. This means that more recruited alveoli participate in gas exchange, thus leading to improved oxygenation due to a decrease in shunt with improved V'/Q' ratios, and increased functional residual capacity with an increase in compliance and a decrease of the work of breathing.

The effects of CPAP on the respiratory system were demonstrated in patients with ARF admitted to an ICU with acute CPO [37, 38]. The application of higher levels of PEEP yielded a decrease in transpulmonary pressure and a parallel decrease in pulmonary pressure. Higher PEEP values were associated with greater levels of oxygenation and decrease of intrapulmonary shunt.

More recently, L'Her *et al.* [39] evaluated the effect of PEEP in 10 patients with acute lung injury, seven of whom had pneumonia. This study compared the short-term effect of CPAP at 10 cmH_2O (CPAP-10) and two combinations of NIV with pressure-support ventilation (PSV): an inspiratory support level of 10 cmH_2O with PEEP of 10 cmH_2O (PSV 10-10) and an inspiratory support level of 15 cmH_2O with PEEP of 5 cmH_2O (PSV 15-5). Compared with spontaneous breathing, the respiratory frequency decreased with the highest levels of inspiratory support (PSV 15-5). In contrast, arterial oxygenation improved similarly with CPAP-10 and PSV 10-10, while this increase failed to reach statistical significance for PSV 15-5. Additionally, the work of breathing decreased with both modalities of NIV but not with CPAP (fig. 3), although the highest reduction in dyspnoea was achieved with PSV 15-5. According to the observed variations in airway pressure in some patients from this study, it could be considered that CPAP was not fairly administered by the ventilator. The authors conclude that whether a different system or type of administration (high-flow CPAP *versus* ventilator; helmet *versus* face-mask) would give different results may warrant further investigation.

Similarly, a recent randomised clinical trial showed that helmet CPAP improved arterial oxygenation more rapidly and efficiently than Venturi oxygen therapy, in patients with CAP and moderate-to-severe hypoxaemia [40]. However, the improvement of oxygenation disappeared 1 h after CPAP was discontinued, suggesting that PEEP is rapidly effective but should be applied for

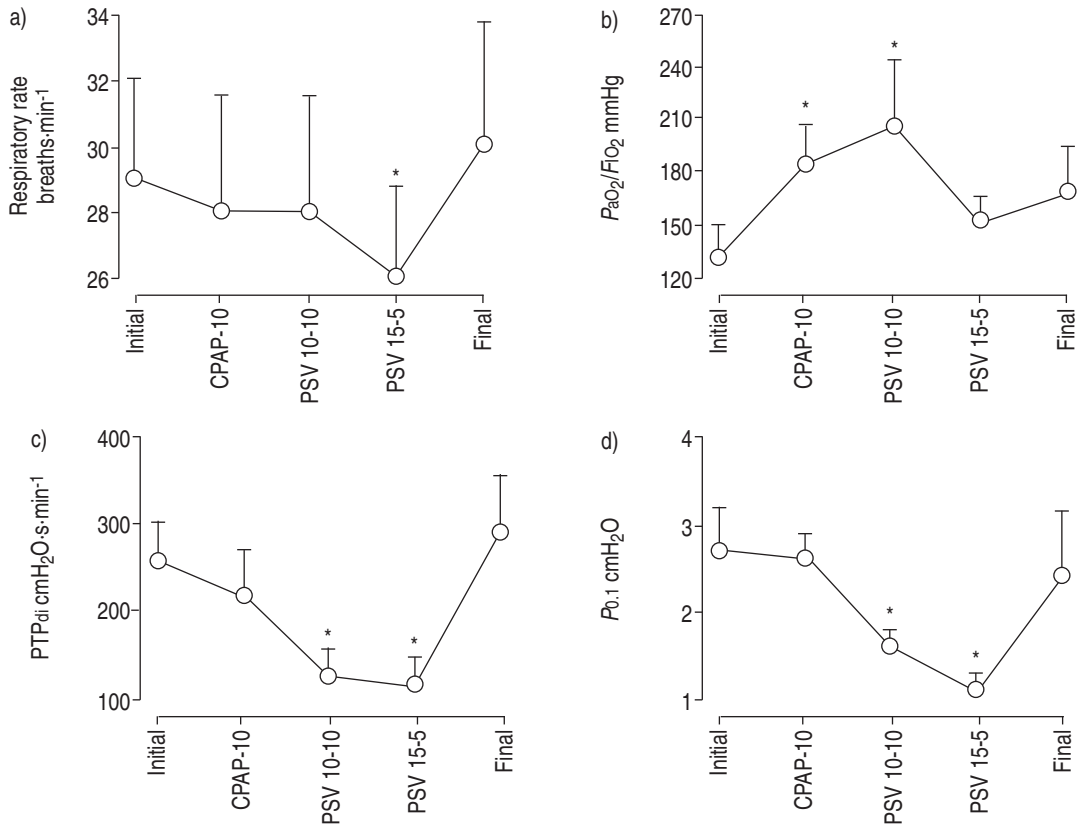


Figure 3. Average changes in respiratory variables. a) Respiratory rate, b) arterial hypoxaemia, assessed by the ratio of arterial oxygen tension (P_{aO_2}) to inspiratory oxygen fraction (F_{IO_2}), c) work of breathing, assessed by the pressure-time product of the diaphragm (PTP_{di}), and d) respiratory drive, assessed by the occlusion pressure ($P_{0.1}$), comparing the initial and final values during spontaneous breathing with the three ventilatory modalities: continuous positive airway pressure (CPAP) at 10 cmH_2O (CPAP-10), pressure-support ventilation (PSV) at 10 cmH_2O with positive end-expiratory pressure (PEEP) of 10 cmH_2O (PSV 10-10), and PSV at 15 cmH_2O with PEEP of 5 cmH_2O (PSV 15-5). *: $p<0.05$, classed as significant differences between initial values and the specific ventilatory modality. Data from [39].

longer periods to obtain clinically relevant effects. A similar effect on oxygenation was observed in a mixed population including patients with CAP and acute CPO [41].

Effects of CPAP on circulation

The circulatory effects of CPAP have been studied mainly in patients with congestive heart failure and acute CPO. The increased intrathoracic pressure induced by the application of PEEP decreases venous return that is usually elevated in patients with heart failure, especially in those with reduced ejection fraction. Moreover, the increase of intrathoracic pressure reduces transmural left ventricular systolic pressure and consequently decreases ventricular afterload [42]. This may produce an increase in cardiac output. In patients with acute CPO with diastolic dysfunction, the increase of intrathoracic pressure induced by CPAP results in a decreased left ventricular end-diastolic volume, *i.e.* preload [42].

The cardiovascular effects of CPAP in patients with pneumonia are less known. The decrease of venous return induced by PEEP application might impair stroke volume in patients who are frequently febrile and relatively or absolutely hypovolaemic, potentially decreasing tissue oxygen delivery. However, in the study by COSENTINI *et al.* [40], systolic and diastolic blood pressure,

Table 2. Cardiovascular effects of continuous positive airway pressure (CPAP) in patients with community-acquired pneumonia

Cardiovascular findings	Time	CPAP		Controls[#]		p-value
		Mean±SD	Patients n	Mean±SD	Patients n	
Systolic BP mmHg	Baseline	132±26	18	135±22	25	0.41
	1 h	127±13	9	127±16	11	
Diastolic BP mmHg	Baseline	78±14	18	73±12	25	0.79
	1 h	74±7.4	9	75±8.9	11	
Heart rate beats·min^{-1}	Baseline	89±15	20	94±16	25	0.19
	1 h	84±12	12	93±18	13	

BP: blood pressure. [#]: treated with oxygen therapy. Reproduced and modified from [40] with permission from the publisher.

together with heart rate, were not significantly modified after 1 h of CPAP or Venturi mask oxygen administration (table 2).

Data on systolic blood pressure and heart rate were analysed by DELCLAUX *et al.* [41]. Heart rate significantly decreased in both groups at 1 h in the ICU, without differences between CPAP and oxygen therapy. Conversely, systolic blood pressure was unchanged after 1 h in the ICU in both groups.

In summary, the demonstrated effect of venous return decrease with PEEP application should alert physicians to monitor the haemodynamic effects when CPAP is considered an option to treat a patient with ARF secondary to pneumonia. Patients' volume should always be assessed before CPAP application, and fluids should be reasonably administered to counterbalance the expected effects of PEEP on intrathoracic and circulating volume.

CPAP in immunosuppressed patients

The first attempts to apply positive pressure ventilation in immunosuppressed patients were made in the late 1980s and early 1990s using CPAP, mainly in patients with AIDS and with ARF due to *Pneumocystis jiroveci* infection [43–47]. All these studies, although uncontrolled, showed an improvement in arterial oxygenation without major complications attributed to CPAP, and concluded that CPAP delivered *via* a nasal or face mask was an effective supportive therapy in these acutely ill patients. The authors highlighted that attention should be paid to the possible occurrence of pneumothorax.

Acute lung injury is very common during the course of haematological malignancy. HILBERT *et al.* [48] published in 2000 a 5-year prospective study on CPAP efficacy in the treatment of febrile neutropenic patients with ARF. CPAP was successful in avoiding endotracheal intubation in 16 out of 64 patients. All 16 responders and four nonresponders survived. In the multivariate analysis, worse severity scores and hepatic failure at the entry into the study were predictive of CPAP failure.

More recently, PRINCIPI *et al.* [49] described the use of CPAP directly in the haematological unit of a university hospital. They compared the efficacy of early administration of noninvasive CPAP delivered by the helmet *versus* face mask in historical matched controls to treat haematological malignancy patients with fever, pulmonary infiltrates and hypoxaemic ARF. Oxygenation improved in all 34 patients after noninvasive CPAP. No patient failed helmet CPAP because of intolerance while eight patients in the mask group did so. CPAP could be applied continuously for a longer period of time in the helmet group. The authors concluded that early CPAP with helmet improves oxygenation in selected immunosuppressed patients with hypoxaemic ARF even outside the ICU. Indeed, the tolerance of helmet CPAP seems better than that of CPAP delivered by mask.

The efficacy of early CPAP *versus* oxygen alone was evaluated in a prospective randomised clinical trial by SQUADRONE *et al.* [50]. The authors enrolled 40 consecutive neutropenic patients with radiological evidence of bilateral pulmonary infiltrates, ARF and respiratory rate

>25 breaths·min^{-1}. They were randomised to control (oxygen through Venturi mask at F_{IO_2} 0.50) or helmet CPAP (F_{IO_2} 0.50 plus PEEP 10 cmH_2O). Patients who received CPAP had less need of ICU admission for mechanical ventilation; among patients admitted to the ICU, the intubation rate was lower in the CPAP than in the control group. The authors suggested that the early use of CPAP on the haematological ward in patients with early changes in respiratory variables prevents evolution to acute lung injury requiring mechanical ventilation and ICU admission.

In summary, CPAP application for the treatment of ARF in immunosuppressed patients seems effective in terms of physiological variables and the reduction of endotracheal intubation and mortality.

CPAP in immunocompetent patients

Initial uncontrolled case reports on the application of CPAP in the treatment of severe ARF in immunocompetent patients with influenza [51] and chickenpox pneumonia [52] showed favourable results without associated complications.

The first randomised clinical trial comparing CPAP with oxygen alone enrolled 123 consecutive patients admitted to six ICUs with severe ARF [41]. This population consisted of patients with pneumonia in 54% and acute CPO in the remaining cases. This study showed that, despite an initial greater improvement of oxygenation in patients treated with CPAP compared with patients with oxygen alone (fig. 4), CPAP reduced neither the need for intubation, the length of stay nor the mortality. In addition, a higher number of adverse events occurred with CPAP treatment. However, a large proportion of patients enrolled met the definition of ARDS, which is a known negative prognostic factor of hypoxaemic ARF [19]. Besides this, among the 61 patients randomised to oxygen alone, five (8%) were switched to CPAP but the authors did not indicate whether their outcome was attributed to the initial treatment arm. Since this trial was in a heterogeneous population mainly suffering from ARDS, these data add limited evidence-based information on the efficacy of CPAP in pneumonia.

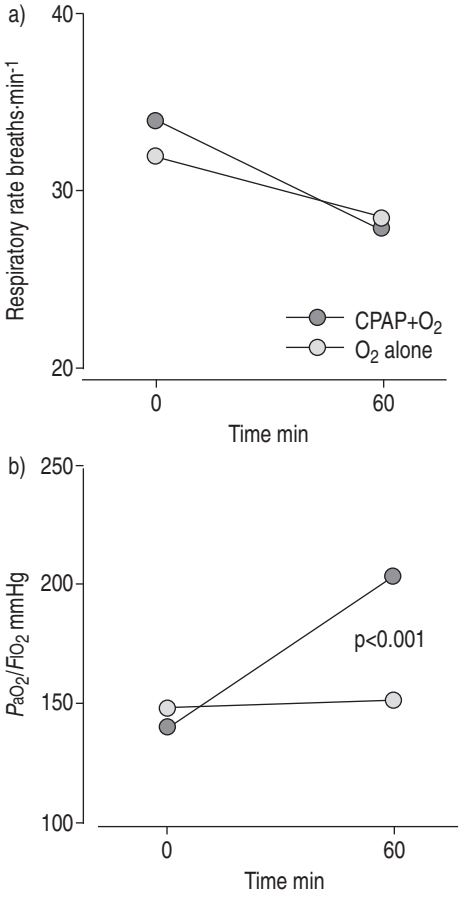


Figure 4. Initial evolution of a) respiratory rate and b) arterial hypoxaemia, assessed by the ratio of arterial oxygen tension (P_{aO_2}) to inspiratory oxygen fraction (F_{IO_2}). Patients were treated either with continuous positive airway pressure (CPAP) plus oxygen or with oxygen alone. Data are shown at baseline and 60 min after the initiation of treatment. $p<0.001$ for comparison of P_{aO_2}/F_{IO_2} between treatment groups. Data from [41].

Based on the previous randomised clinical trial on patients with pneumonia and moderate-to-severe hypoxaemia that showed a better improvement in oxygenation with helmet CPAP [40], a new multicentre randomised clinical trial has compared helmet CPAP application to oxygen alone in patients with pneumonia with severe ARF. The preliminary report of this trial showed that noninvasive CPAP delivered by a helmet reduces the risk of meeting intubation criteria in comparison to oxygen therapy, from 60% to 12.5%, in patients with severe ARF due to pneumonia [53].

In summary, the evidence-based data provided by the literature on CPAP application in pneumonia is more consistent in immunosuppressed patients, where the application of NIV is also generally strongly recommended. However, in the immunocompetent

population, prospective randomised clinical trials on CPAP use are very few and the design, results and conclusions of some of them are debatable. The only data where all trials are concordant relate to the common observation that CPAP application improves gas exchange and physiological variables. However, until reliable well designed controlled studies are available, the question of whether CPAP is useful in patients with pneumonia is still open.

Invasive mechanical ventilation

IMV due to life-threatening respiratory failure is a major determinant for ICU admission in hospitalised patients with CAP [1, 25]. Between 37% and 60% patients with severe CAP admitted to the ICU require IMV [25, 54–56]. However, the use of IMV presents multiple complications [57, 58] and has been associated with a high mortality in patients with CAP [59]. Studies have reported mortality rates associated with ICU admission ranging between 13% and 28%, depending on the different series and whether ICU or hospital mortality rates were reported [25, 54–56].

In general, intubation and institution of IMV should be considered in the presence of the following criteria [23]: 1) respiratory or cardiac arrest; 2) severe respiratory failure plus respiratory pauses with loss of consciousness or gasping for air; 3) psychomotor agitation inadequately controlled by sedation; 4) massive aspiration; 5) persistent inability to remove respiratory secretions; 6) heart rate <50 beats·min^{-1} with loss of alertness; 7) severe haemodynamic instability without response to fluids and vasoactive drugs; 8) evidence for exhaustion, such as active contraction of the accessory muscles with thoracic-abdominal paradoxical movement; 9) severely decreased consciousness due to evident or suspected cranial hypertension or risk of aspiration; 10) obstruction or instability of upper airway; or 11) cardiac arrhythmia with low tissue perfusion.

A recent study showed that IMV was used more frequently than NIV in hospitalised patients with CAP [60]. Among 2423 consecutive, hospitalised patients with CAP, 101 (4%) required IMV and 68 (3%) required NIV in this study. In contrast with the large amount of information regarding the use of NIV in patients with CAP and severe ARF [12], the available specific information on the use of IMV in hospitalised patients with CAP is limited, without reports that have systematically and specifically assessed the use of IMV in large series of patients with CAP.

Given the limited specific information on patients hospitalised with CAP treated with IMV for an episode of severe ARF, we prospectively assessed the characteristics and outcomes of these patients and compared them with patients who needed NIV or no ventilatory support. Among 7715 consecutive patients, 260 (3%) required IMV and 253 (3%) had successful NIV (M. Ferrer; personal communication). This study, which is not yet published, showed that patients with IMV, compared with the other groups, more frequently had methicillin-resistant *Staphylococcus aureus* and less frequently had *Streptococcus pneumoniae* and atypical bacteria as aetiological agents of pneumonia. Current smoking, dyspnoea, worse oxygenation and higher Pneumonia Severity Index (PSI) risk class at admission were independent predictors of needing IMV, while former tobacco consumption, pneumococcal vaccination and cough at admission were independently associated with no need for IMV. Diabetes mellitus, dyspnoea, higher levels of C-reactive protein, worse oxygenation and higher PSI risk class at admission were independent predictors of needing NIV, while previous influenza vaccination and fever at admission were independently associated with no need for NIV. As expected, the 30-day mortality was highest in the IMV group, followed by the NIV group and nonventilated patients. While the need for ventilatory support was associated with more severe clinical presentation at admission, both the need for NIV and IMV, among others, were independently associated with increased 30-day mortality.

This study highlighted that several variables at admission independently associated with need for IMV, such as active smoking, absence of cough, worse hypoxaemia and higher PSI risk scales, may help in the early detection of patients at risk of deterioration in order to allocate them to appropriate facilities such as an ICU or intermediate care unit. This is particularly important, since delayed ICU admission for any cause may occur in at least 30% patients with severe CAP [61].

Delayed ICU admission in these patients was associated with 2–2.6-fold increased risk for hospital mortality in two studies, compared with direct admission from the emergency room [61, 62]. The proper use of resources for critically ill patients is important to avoid either the unnecessary occupation of ICU beds or the increased mortality associated with delayed ICU admission.

The association of worse oxygenation with poor outcome has already been highlighted in a prospective study [63]. This study also found that a progressive improvement of PaO_2/FIO_2 ratio during the first 48 h of mechanical ventilation indicates favourable outcome. The authors advised the consideration of serial measurement of this ratio in decision making for therapeutic strategy.

Several studies have assessed predictors of outcome in patients with CAP who require IMV [64–67]. These studies were retrospective or, in one case, prospective historic data were analysed [65], and included a limited number of patients, ranging between 85 and 124. The mortality rate of these patients was high: 32% and 55% for ICU mortality [64, 67], and 46% and 56% for hospital mortality [65, 66]. More advanced age, comorbidities and higher severity scores of pneumonia and organ system dysfunction at admission were independently associated with mortality in these studies. However, these studies were restricted to ventilated patients and therefore no information on predictors for the need for IMV was reported.

Extracorporeal lung support

Extracorporeal lung support may be considered when patients do not respond favourably even under maximal ventilatory support. Extracorporeal membrane oxygenation (ECMO) was proposed soon after its first description as a possible management option for the most hypoxaemic cases of ARDS, but two randomised clinical trials could not confirm the superiority of the technique over more conventional management [68, 69], and its use was long restricted to a few selected centres. Renewed interest in this therapy has been stimulated by technical improvements and by the positive results of a more recent randomised clinical trial [70]. This technique was thus more widely used during the recent influenza A H1N1 pandemic as a rescue therapy for the most severe cases that met ARDS criteria who could barely be managed with conventional therapy, with generally acceptable outcomes for the patients [71–73]. In these cases, ECMO requires an ultraprotective ventilation strategy minimising plateau pressure in order to improve outcome. However, when patients with severe influenza A H1N1-related ARDS treated with ECMO were compared with conventionally treated patients, no difference in mortality rates existed in a propensity-matched analysis [73]. Studies and meta-analyses often report that patients treated with ECMO due to ARDS secondary to severe influenza A H1N1 are younger and have few comorbidities [71, 73]. A recent meta-analysis concluded that ECMO is feasible and effective in patients with acute lung injury due to H1N1 infection [74]. Despite this, prolonged support, often more than 1 week, is required in most cases, and subjects with severe comorbidities or multiorgan failure remain at high risk of death.

In recent years, several case series of patients with pneumonia and severe ARDS criteria have been published [75–77]. These prospective, uncontrolled studies have generally reported favourable outcomes associated with the use of ECMO. However, no randomised clinical trials have been specifically conducted in patients with CAP and severe ARF.

In general, the use of ECMO in patients with ARDS should be considered in the presence of one or more of the following: severe hypoxaemia (*e.g.* PaO_2/FIO_2 <80 mmHg, despite the application of high levels of PEEP in patients with potentially reversible respiratory failure), uncompensated hypercapnia with acidaemia (PH <7.15), and the presence of excessively high end-inspiratory plateau pressures (>35–45 cmH_2O, according to the patient's body size), despite the best accepted standard of care for management with a ventilator [75]. Patients requiring mechanical ventilation with a high end-inspiratory plateau pressure (>30 cmH_2O) or a high FIO_2 (>0.80) for more than 7 days may be less likely to benefit from ECMO. Further contraindications are limited vascular

access, any condition or organ dysfunction that would limit the likelihood of overall benefit from ECMO, and any condition that precludes the use of anticoagulation therapy [75]. Earlier initiation has been associated with better outcomes in some, but not all, observational studies.

Conclusions

The cornerstone for the treatment of CAP remains a timely and appropriate antimicrobial treatment. Figure 5 shows a proposed algorithm for the use of supportive measures in CAP with ARF.

In the least severe cases of ARF, oxygen therapy is the appropriate support. The assessment of severity should include arterial oxygenation and respiratory rate. Monitoring of patients is advised in the presence of dyspnoea at rest, decreased consciousness, severe tachypnoea, cyanosis and signs of respiratory muscle fatigue. The encouraging clinical results still generate debate about the use of NIV, mainly because of safety issues. NIV is discouraged unless shock, metabolic acidosis and severe hypoxaemia are rapidly resolved. The high rate of NIV failure suggests a cautious approach to NIV use, including early initiation, close monitoring and prompt intubation if signs of NIV failure emerge. Patients with previous cardiac or respiratory disease or hypoxaemic patients with single organ failure seem to be the safest and most appropriate population for NIV treatment. The helmet is a promising interface for the use of NIV, particularly in hypoxaemic nonhypercapnic patients. The benefits of the use of CPAP in pneumonia are more consistent in immunosuppressed patients. IMV remains the standard of care in cases of life-threatening respiratory failure and in cases of multiple organ system

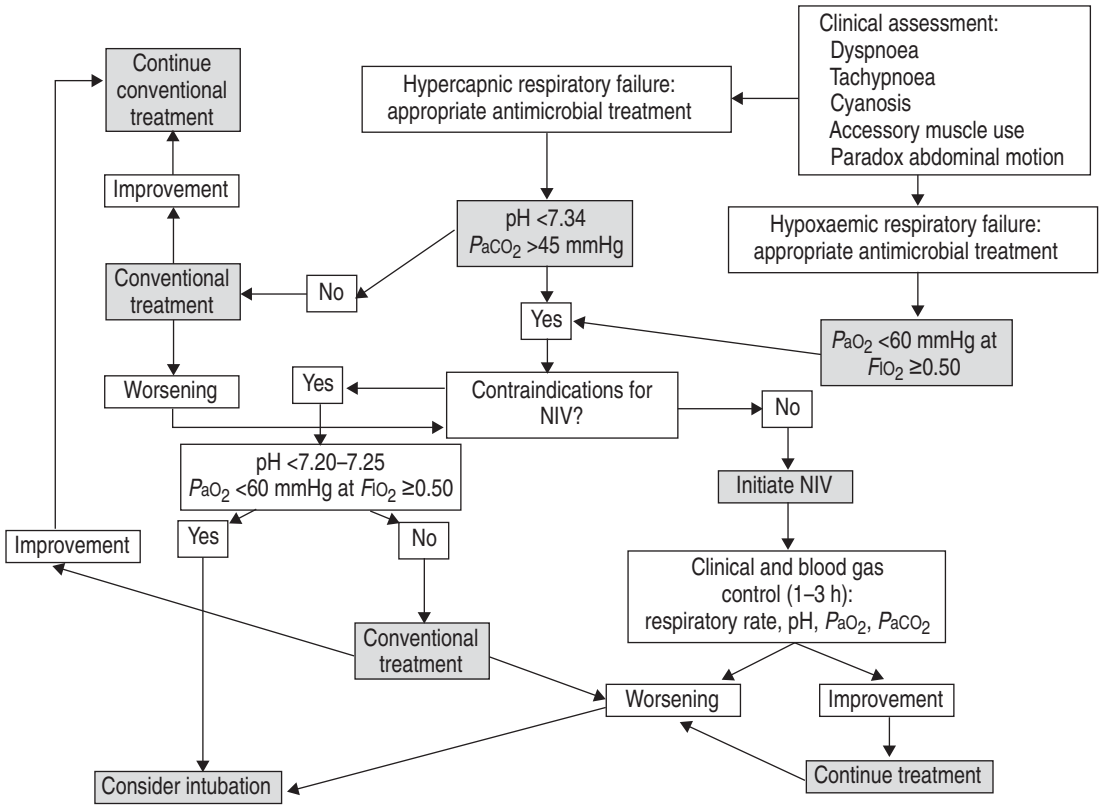


Figure 5. Proposed algorithm for the use of supportive measures in patients with community-acquired pneumonia and acute respiratory failure. P_{aCO_2}: arterial carbon dioxide tension; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; NIV: noninvasive ventilation.

dysfunction. Extracorporeal life support, a rescue therapy restricted to cases who do not respond favourably under maximal ventilatory support, has shown promising results in patients with pandemic H1N1 influenza pneumonia.

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Statement of Interest

None declared.

References

1. Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44: Suppl. 2, S27–S72.
2. Restrepo MI, Anzueto A. Severe community-acquired pneumonia. *Infect Dis Clin North Am* 2009; 23: 503–520.
3. Oosterheert JJ, Bonten MJ, Hak E, *et al.* Severe community-acquired pneumonia: what's in a name? *Curr Opin Infect Dis* 2003; 16: 153–159.
4. Ewig S, Woodhead M, Torres A. Towards a sensible comprehension of severe community-acquired pneumonia. *Intensive Care Med* 2011; 37: 214–223.
5. Gea J, Roca J, Torres A, *et al.* Mechanisms of abnormal gas exchange in patients with pneumonia. *Anesthesiology* 1991; 75: 782–789.
6. Lampron N, Lemaire F, Teisseire B, *et al.* Mechanical ventilation with 100% oxygen does not increase intrapulmonary shunt in patients with severe bacterial pneumonia. *Am Rev Respir Dis* 1985; 131: 409–413.
7. Melot C. Contribution of multiple inert gas elimination technique to pulmonary medicine. 5. Ventilation-perfusion relationships in acute respiratory failure. *Thorax* 1994; 49: 1251–1258.
8. Graham LM, Vasil A, Vasil ML, *et al.* Decreased pulmonary vasoreactivity in an animal model of chronic *Pseudomonas* pneumonia. *Am Rev Respir Dis* 1990; 142: 221–229.
9. Light RB, Mink SN, Wood LD. Pathophysiology of gas exchange and pulmonary perfusion in pneumococcal lobar pneumonia in dogs. *J Appl Physiol Respir Environ Exerc Physiol* 1981; 50: 524–530.
10. Torres A, Serra-Batlles J, Ferrer A, *et al.* Severe community-acquired pneumonia. Epidemiology and prognostic factors. *Am Rev Respir Dis* 1991; 144: 312–318.
11. Pierson DJ. Indications for mechanical ventilation in adults with acute respiratory failure. *Respir Care* 2002; 47: 249–262.
12. Ferrer M, Cosentini R, Nava S. The use of non-invasive ventilation during acute respiratory failure due to pneumonia. *Eur J Intern Med* 2012; 23: 420–428.
13. Wijesinghe M, Perrin K, Healy B, *et al.* Randomized controlled trial of high concentration oxygen in suspected community-acquired pneumonia. *J R Soc Med* 2012; 105: 208–216.
14. Lightowler JV, Wedzicha JA, Elliott MW, *et al.* Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *BMJ* 2003; 326: 185–189.
15. Weng CL, Zhao YT, Liu QH, *et al.* Meta-analysis: Noninvasive ventilation in acute cardiogenic pulmonary edema. *Ann Intern Med* 2010; 152: 590–600.
16. Girou E, Schortgen F, Delclaux C, *et al.* Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. *JAMA* 2000; 284: 2361–2367.
17. Meade MO, Cook DJ, Kernerman P, *et al.* How to use articles about harm: the relationship between high tidal volumes, ventilating pressures, and ventilator-induced lung injury. *Crit Care Med* 1997; 25: 1915–1922.
18. Keenan SP, Sinuff T, Cook DJ, *et al.* Does noninvasive positive pressure ventilation improve outcome in acute hypoxemic respiratory failure? A systematic review. *Crit Care Med* 2004; 32: 2516–2523.
19. Antonelli M, Conti G, Moro ML, *et al.* Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive Care Med* 2001; 27: 1718–1728.
20. Confalonieri M, Potena A, Carbone G, *et al.* Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. *Am J Respir Crit Care Med* 1999; 160: 1585–1591.
21. Jolliet P, Abajo B, Pasquina P, *et al.* Non-invasive pressure support ventilation in severe community-acquired pneumonia. *Intensive Care Med* 2001; 27: 812–821.
22. Domenighetti G, Gayer R, Gentilini R. Noninvasive pressure support ventilation in non-COPD patients with acute cardiogenic pulmonary edema and severe community-acquired pneumonia: acute effects and outcome. *Intensive Care Med* 2002; 28: 1226–1232.

23. Ferrer M, Esquinas A, Leon M, *et al.* Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. *Am J Respir Crit Care Med* 2003; 168: 1438–1444.
24. Demoule A, Girou E, Richard JC, *et al.* Benefits and risks of success or failure of noninvasive ventilation. *Intensive Care Med* 2006; 32: 1756–1765.
25. Liapikou A, Ferrer M, Polverino E, *et al.* Severe community-acquired pneumonia: validation of the Infectious Diseases Society of America/American Thoracic Society guidelines to predict an intensive care unit admission. *Clin Infect Dis* 2009; 48: 377–385.
26. Aliberti S, Amir A, Peyrani P, *et al.* Incidence, etiology, timing, and risk factors for clinical failure in hospitalized patients with community-acquired pneumonia. *Chest* 2008; 134: 955–962.
27. Carrillo A, Gonzalez-Diaz G, Ferrer M, *et al.* Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure. *Intensive Care Med* 2012; 38: 458–466.
28. Carron M, Freo U, Zorzi M, *et al.* Predictors of failure of noninvasive ventilation in patients with severe community-acquired pneumonia. *J Crit Care* 2010; 25: 540.e9–540.e14.
29. Ambrosino N, Foglio K, Rubini F, *et al.* Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: correlates for success. *Thorax* 1995; 50: 755–757.
30. Rana S, Jenad H, Gay PC, *et al.* Failure of non-invasive ventilation in patients with acute lung injury: observational cohort study. *Crit Care* 2006; 10: R79.
31. Goldhill DR, Sumner A. Outcome of intensive care patients in a group of British intensive care units. *Crit Care Med* 1998; 26: 1337–1345.
32. Goldhill DR, Withington PS. The effect of casemix adjustment on mortality as predicted by APACHE II. *Intensive Care Med* 1996; 22: 415–419.
33. Masclans JR, Perez M, Almirall J, *et al.* Early non-invasive ventilation treatment for severe influenza pneumonia. *Clin Microbiol Infect* 2013; 19: 249–256.
34. Rabitsch W, Staudinger T, Locker GJ, *et al.* Respiratory failure after stem cell transplantation: improved outcome with non-invasive ventilation. *Leuk Lymphoma* 2005; 46: 1151–1157.
35. Antonelli M, Conti G, Bufi M, *et al.* Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. *JAMA* 2000; 283: 235–241.
36. Hilbert G, Gruson D, Vargas F, *et al.* Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med* 2001; 344: 481–487.
37. Räsänen J, Väisänen IT, Heikkilä J, *et al.* Acute myocardial infarction complicated by left ventricular dysfunction and respiratory failure. The effects of continuous positive airway pressure. *Chest* 1985; 87: 158–162.
38. Lenique F, Habis M, Lofaso F, *et al.* Ventilatory and hemodynamic effects of continuous positive airway pressure in left heart failure. *Am J Respir Crit Care Med* 1997; 155: 500–505.
39. L'Her E, Deye N, Lellouche F, *et al.* Physiologic effects of noninvasive ventilation during acute lung injury. *Am J Respir Crit Care Med* 2005; 172: 1112–1118.
40. Cosentini R, Brambilla AM, Aliberti S, *et al.* Helmet continuous positive airway pressure *vs* oxygen therapy to improve oxygenation in community-acquired pneumonia: a randomized, controlled trial. *Chest* 2010; 138: 114–120.
41. Delclaux C, L'Her E, Alberti C, *et al.* Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: a randomized controlled trial. *JAMA* 2000; 284: 2352–2360.
42. Bendjelid K, Schütz N, Suter PM, *et al.* Does continuous positive airway pressure by face mask improve patients with acute cardiogenic pulmonary edema due to left ventricular diastolic dysfunction? *Chest* 2005; 127: 1053–1058.
43. Kesten S, Rebuck AS. Nasal continuous positive airway pressure in *Pneumocystis carinii* pneumonia. *Lancet* 1988; 2: 1414–1415.
44. Gregg RW, Friedman BC, Williams JF, *et al.* Continuous positive airway pressure by face mask in *Pneumocystis carinii* pneumonia. *Crit Care Med* 1990; 18: 21–24.
45. Miller RF, Semple SJ. Continuous positive airway pressure ventilation for respiratory failure associated with *Pneumocystis carinii* pneumonia. *Respir Med* 1991; 85: 133–138.
46. Prevedoros HP, Lee RP, Marriot D. CPAP, effective respiratory support in patients with AIDS-related *Pneumocystis carinii* pneumonia. *Anaesth Intensive Care* 1991; 19: 561–566.
47. Gachot B, Clair B, Wolff M, *et al.* Continuous positive airway pressure by face mask or mechanical ventilation in patients with human immunodeficiency virus infection and severe *Pneumocystis carinii* pneumonia. *Intensive Care Med* 1992; 18: 155–159.
48. Hilbert G, Gruson D, Vargas F, *et al.* Noninvasive continuous positive airway pressure in neutropenic patients with acute respiratory failure requiring intensive care unit admission. *Crit Care Med* 2000; 28: 3185–3190.
49. Principi T, Pantanetti S, Catani F, *et al.* Noninvasive continuous positive airway pressure delivered by helmet in hematological malignancy patients with hypoxemic acute respiratory failure. *Intensive Care Med* 2004; 30: 147–150.
50. Squadrone V, Massaia M, Bruno B, *et al.* Early CPAP prevents evolution of acute lung injury in patients with hematologic malignancy. *Intensive Care Med* 2010; 36: 1666–1674.
51. Taylor GJ, Brenner W, Summer WR. Severe viral pneumonia in young adults. *Chest* 1976; 69: 722–728.
52. Pillans P. Chickenpox pneumonia. A case report. *S Afr Med J* 1983; 63: 861–862.
53. Prina E, Brambilla AM, Aliberti S, *et al.* Non-invasive continuous positive airway pressure *versus* oxygen venturi in severe acute respiratory failure due to pneumonia: a randomized controlled trial. *Eur Respir J* 2013; 42: Suppl. 57, 1017s.

54. Leroy O, Santre C, Beuscart C, *et al.* A five-year study of severe community-acquired pneumonia with emphasis on prognosis in patients admitted to an intensive care unit. *Intensive Care Med* 1995; 21: 24–31.
55. Bodi M, Rodriguez A, Sole-Violan J, *et al.* Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to Infectious Diseases Society of America guidelines on survival. *Clin Infect Dis* 2005; 41: 1709–1716.
56. Restrepo MI, Mortensen EM, Velez JA, *et al.* A comparative study of community-acquired pneumonia patients admitted to the ward and the ICU. *Chest* 2008; 133: 610–617.
57. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002; 165: 867–903.
58. Pinhu L, Whitehead T, Evans T, *et al.* Ventilator-associated lung injury. *Lancet* 2003; 361: 332–340.
59. Leeper KV Jr, Torres A. Community-acquired pneumonia in the intensive care unit. *Clin Chest Med* 1995; 16: 155–171.
60. Prina E, Ferrer M, Ranzani OT, *et al.* Thrombocytosis is a marker of poor outcome in community-acquired pneumonia. *Chest* 2013; 143: 767–775.
61. Renaud B, Santin A, Coma E, *et al.* Association between timing of intensive care unit admission and outcomes for emergency department patients with community-acquired pneumonia. *Crit Care Med* 2009; 37: 2867–2874.
62. Restrepo MI, Mortensen EM, Rello J, *et al.* Late admission to the ICU in patients with community-acquired pneumonia is associated with higher mortality. *Chest* 2010; 137: 552–557.
63. Wu CL, Lin FJ, Lee SY, *et al.* Early evolution of arterial oxygenation in severe community-acquired pneumonia: a prospective observational study. *J Crit Care* 2007; 22: 129–136.
64. Tejerina E, Frutos-Vivar F, Restrepo MI, *et al.* Prognosis factors and outcome of community-acquired pneumonia needing mechanical ventilation. *J Crit Care* 2005; 20: 230–238.
65. Pascual FE, Matthay MA, Bacchetti P, *et al.* Assessment of prognosis in patients with community-acquired pneumonia who require mechanical ventilation. *Chest* 2000; 117: 503–512.
66. Lee JH, Ryu YJ, Chun EM, *et al.* Outcomes and prognostic factors for severe community-acquired pneumonia that requires mechanical ventilation. *Korean J Intern Med* 2007; 22: 157–163.
67. Aydogdu M, Ozyilmaz E, Aksoy H, *et al.* Mortality prediction in community-acquired pneumonia requiring mechanical ventilation; values of pneumonia and intensive care unit severity scores. *Tuberk Toraks* 2010; 58: 25–34.
68. Zapol WM, Snider MT, Hill JD, *et al.* Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA* 1979; 242: 2193–2196.
69. Morris AH, Wallace CJ, Menlove RL, *et al.* Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994; 149: 295–305.
70. Peek GJ, Mugford M, Tiruvoipati R, *et al.* Efficacy and economic assessment of conventional ventilatory support *versus* extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009; 374: 1351–1363.
71. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, et al. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. *JAMA* 2009; 302: 1888–1895.
72. Patroniti N, Zangrillo A, Pappalardo F, *et al.* The Italian ECMO network experience during the 2009 influenza A (H1N1) pandemic: preparation for severe respiratory emergency outbreaks. *Intensive Care Med* 2011; 37: 1447–1457.
73. Pham T, Combes A, Roze H, *et al.* Extracorporeal membrane oxygenation for pandemic influenza A (H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med* 2013; 187: 276–285.
74. Zangrillo A, Biondi-Zoccai G, Landoni G, *et al.* Extracorporeal membrane oxygenation (ECMO) in patients with H1N1 influenza infection: a systematic review and meta-analysis including 8 studies and 266 patients receiving ECMO. *Crit Care* 2013; 17: R30.
75. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med* 2011; 365: 1905–1914.
76. Hermans G, Meersseman W, Wilmer A, *et al.* Extracorporeal membrane oxygenation: experience in an adult medical ICU. *Thorac Cardiovasc Surg* 2007; 55: 223–228.
77. Bryner B, Miskulin J, Smith C, *et al.* Extracorporeal life support for acute respiratory distress syndrome due to severe *Legionella* pneumonia. *Perfusion* 2014; 29: 39–43.

Chapter 14

Early recognition and treatment of severe sepsis and septic shock in CAP

Anja Kathrin Jaehne, Namita Jayaprakash, Gina Hurst, Steven Moore, Michael F. Harrison and Emanuel P. Rivers

SUMMARY: Community-acquired pneumonia is one of the most common causes of severe sepsis and septic shock, accounting for up to 45% of cases admitted to hospitals. Early identification and illness severity stratification followed by early intervention using a bundled treatment approach have been shown to improve outcomes. This includes blood cultures before antibiotics, fluid resuscitation with 30 mL·kg^{-1} body weight to target a mean arterial blood pressure of at least 65 mmHg, central venous pressure between 8 and 12 mmHg, and a central venous oxygen saturation of 70% within 6 h of diagnosis. In addition, early and appropriate introduction of ventilator assistance not only improves gas exchange, it further reduces the imbalance between oxygen delivery and utilisation. The mortality reduction is also accompanied by a decrease in duration of mechanical ventilation, vasopressor use, and intensive care unit and hospital length of stay.

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Sepsis is a result of infection and a leading cause of death worldwide. Prevalence rates vary greatly; however, it is estimated that in industrialised countries, the incidence of sepsis ranges from 50 to 300 cases per 100 000 population with a mortality from 20% to 50% [1, 2]. Sepsis is the most common and lethal diagnosis on admission to the hospital [3], represents 2% of all hospitalisations, and is responsible for 17% of in-hospital deaths in the USA [4, 5]. The emergency department is the portal of entry for 52.4–65.1% of patients with severe sepsis and septic shock in the USA; however, in Europe, it is the inpatient ward or general practice unit (51.5%) [6].

The respiratory system is the leading cause of severe sepsis and septic shock (fig. 1) [4, 7, 8]. In the USA, community-acquired pneumonia (CAP) is responsible for 1.2 out of 2.05 million (59%) yearly hospital admissions for sepsis (table 1) [12, 13]. Up to 36% of patients admitted to the hospital with CAP are placed in the intensive care unit (ICU), making it one of the most lethal and costly hospital admissions [14]. The incidence of sepsis is increasing [15] because of patients living longer [8] and with more comorbidities (fig. 2) [9, 16–18].

As accepted standards of care and quality measures have evolved and reduced mortality for acute myocardial infarction [10], stroke [11] and trauma [19], similar approaches are required for severe sepsis and septic shock (table 1) [3, 20]. The implementation of these time-sensitive treatment protocols has led to significant improvements for these diseases in morbidity, mortality and healthcare costs. In 2001, a similar approach to sepsis began when a prospective randomised trial comparing early goal-directed therapy (EGDT) to standard care. This study used specific criteria for the early identification of high-risk patients with severe sepsis and septic shock, with the majority (39%) of patients having CAP [21]. The components of EGDT originated from expert consensus-derived diagnostic and therapeutic interventions in the most proximal phase of disease presentation [22]. After more than a decade, the salutary impact of EGDT on the inflammatory response [23], reducing organ failure [24], mortality [25] and healthcare resource consumption [25, 26] has been replicated in multiple studies.

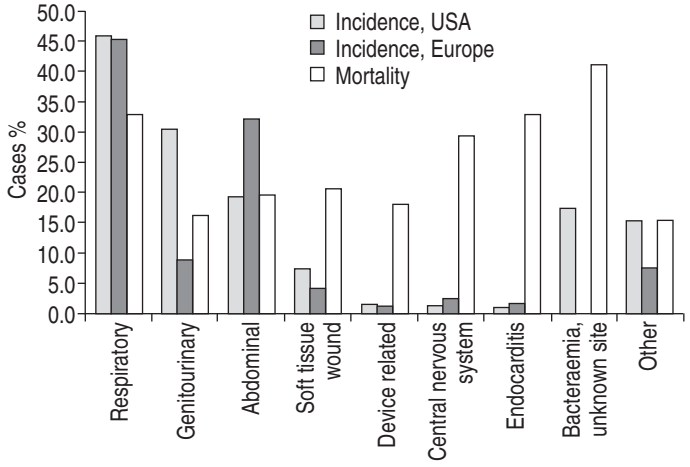

Figure 1. Infectious causes of sepsis in the USA and Europe.

Thus, CAP is the most common cause of severe sepsis and septic shock representing a serious health problem worldwide [27–29]. This chapter will examine the pathogenic principles that provide the foundation of evidence that early application of EGDT or the resuscitation bundle modulates the pathogenesis of systemic inflammation, decreases the progression of organ failure and decreases healthcare resource consumption in patients who present with severe sepsis and septic shock associated with CAP.

The pathophysiology of early sepsis

CAP, a form of sepsis, begins a complex host–pathogen interaction between pro-inflammatory, anti-inflammatory and apoptotic mediators (fig. 3) [31]. These mediator interactions are accompanied by circulatory insufficiency, which includes hypovolaemia, vasodilatation, myocardial depression and increased metabolic demands. The result of this circulatory insufficiency is an imbalance between systemic oxygen supply and demand, leading to global tissue hypoxia. This pathogenic sequence of events significantly contributes to development of organ failure and mortality [32, 33].

Table 1. Mortality of the most frequent diseases presenting to the emergency department in the USA

	Cases per year	Mortality %
Sepsis		
2000 [5]	326 000	
2008 [5]	727 000	
2007–2009 [3]	859 858	20.4
Severe sepsis	300 270	
2000 [4]	711 736–781 725	39.6
2007 [4]	791 000	27.3
Septic shock		
2000 [4, 9]	200 000	45.0–47.1
2007 [4]		36.4
Pneumonia [10]	1 187 180	4.98
Stroke [10]	591 996	6.63
Acute myocardial infarction [3, 10]	540 891	10.03
Trauma [11]		up to 15.6

During shock states, a critical decrease in systemic oxygen delivery

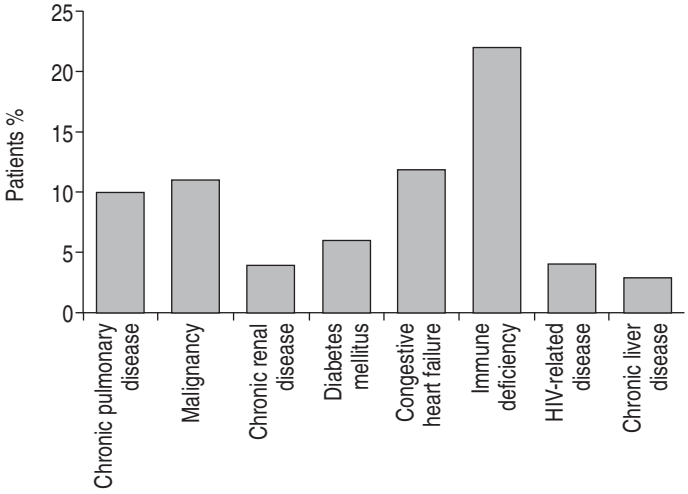

Figure 2. Comorbidities of septic patients.

($D\mathrm{O}_2$) and an increase in systemic oxygen consumption ($V'\mathrm{O}_2$) lead to a decrease in central venous oxygen saturation ($S\mathrm{cvO}_2$) and mixed venous oxygen saturation ($S\mathrm{vO}_2$), and, therefore, an increase in the systemic oxygen extraction ratio (OER). This increase in OER is a compensatory mechanism to match systemic oxygen demands. When the limit of this compensatory mechanism (OER greater than 50–60%) is reached and the oxygen demands of the tissue are not met, anaerobic metabolism ensues, leading to lactate production and a decrease in $S\mathrm{cvO}_2$ and $S\mathrm{vO}_2$ [34]. This phase is frequently associated with acute cardiopulmonary deterioration.

Over 12% of cardiac arrests within the first 24 h of admission to the hospital have an admitting diagnosis of CAP [35]. In the delivery-dependent, or hypodynamic, phase, lactate concentrations are inversely related to $D\mathrm{O}_2$ and $S\mathrm{cvO}_2$ (fig. 4) [36]. This phase can occur with normal vital signs, which is referred to as "occult shock", and is characterised by a significant lactic acidosis (>4 mmol·L^{-1}), despite a normal or even elevated blood pressure. Progression to multisystem organ dysfunction and sudden cardiopulmonary collapse may occur if occult shock is unrecognised or left untreated [32, 37–39]. Thus, early detection of high risk patients is a key to decreasing mortality.

After comprehensive resuscitation, the hypodynamic phase usually transitions to the hyperdynamic phase characterised by an elevated to normal lactate concentration and an increased $S\mathrm{cvO}_2$ denotes a state where $V'\mathrm{O}_2$ is independent of $D\mathrm{O}_2$. This is a normal response in the majority of patients; however, it is pathological in patients with elevated $S\mathrm{cvO}_2$ and lactate levels over time. The failure to increase OER and thus increase $V'\mathrm{O}_2$ may be secondary to impairment in microvascular oxygen perfusion or mitochondrial dysfunction. This has been called microcirculatory and mitochondrial distress syndrome (MMDS) [40]. Although there is an association with increased mortality and MMDS, therapy specifically directed at improving this disorder morphologically has not led to improved outcomes [41].

The association between global tissue hypoxia and inflammation has been well described *in vitro* [42]. Persistent global tissue hypoxia *in vivo*, evidenced by lactate elevation and low $S\mathrm{cvO}_2$, significantly correlates with pro- and anti-inflammatory biomarker activity [23]. EGDT significantly lowers the early (within 12 h) and late peaks (within 24 h) of these biomarkers. These late peaks might relate to a pathogenic mechanism leading to the "second-hit" phenomenon of multiorgan failure [23, 43]. The observation of a 15% reduction in mechanical ventilation [26], and decreased incidence of acute kidney injury [24] and mortality reflects the prevention of this second hit in patients treated with the EGDT protocol.

Risk stratification of illness severity in CAP

The best outcomes are realised when the severity of illness of any disease is accompanied by an evidence-based intervention at the most proximal phase of presentation (tables 2 and 3) [45]. An illness severity or risk stratification tool classifies sepsis using predisposition (age, chronic obstructive pulmonary disease, chronic liver disease, residence in a nursing home, and malignancy with and without metastasis), infection or insult (pneumonia and skin or soft tissue infection or trauma), response (tachypnoea, tachycardia and bandaemia, *via* the inflammatory cascade with

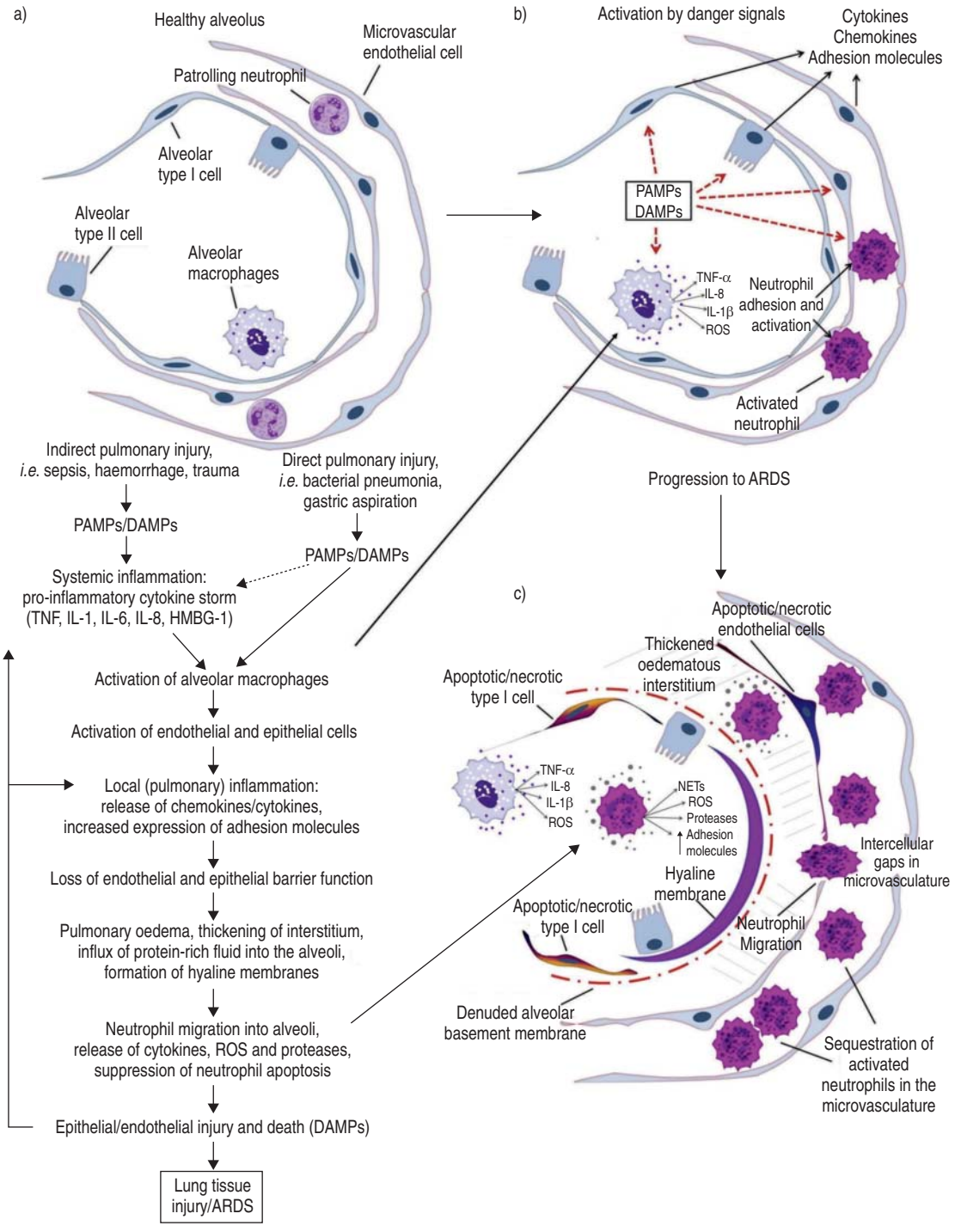

Figure 3. Acute lung injury. The phases of acute respiratory distress syndrome (ARDS) development are shown: a) healthy alveolus; b) early inflammation; c) ARDS. PAMP: pathogen-associated molecular pattern; DAMP: danger-associated molecular pattern; TNF: tumour necrosis factor; IL: interleukin; HMBG: high-mobility group protein B; ROS: reactive oxygen species; NET: neutrophil extracellular trap. Reproduced from [30] with permission from the publisher.

activation of pro- or anti-inflammatory cytokines), and organ failure (renal, respiratory, cardiac and haematological; as a sequela of infection in relation to the uncontrolled inflammatory response) forms the PIRO scoring system [46].

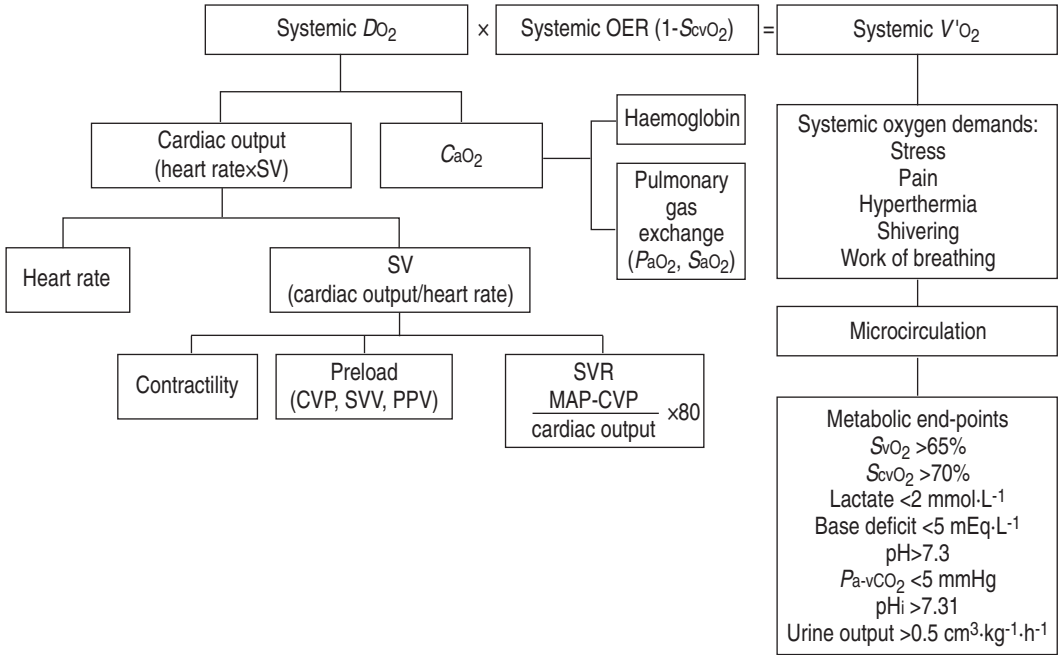

Figure 4. Haemodynamic and metabolic end-points of resuscitation. D_{O_2}: oxygen delivery; SV: stroke volume; CVP: central venous pressure; SVV: stroke volume variation; PPV: pulse pressure variation; SVR: systemic vascular resistance; MAP: mean arterial pressure; C_{aO_2}: arterial oxygen content; P_{aO_2}: arterial oxygen tension; S_{aO_2}: arterial oxygen saturation; OER: oxygen extraction ratio; S_{cvO_2}: central venous oxygen saturation; V'_{O_2}: oxygen consumption; S_{vO_2}: mixed venous oxygen saturation; P_{a-vCO_2}: arterial–venous carbon dioxide tension gradient; pH_i: intracellular pH.

Risk stratification in CAP

Tools specific to CAP, such as the Pneumonia Severity Index (PSI)/Patients Outcomes Research Team score [47], CURB (confusion, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) or ⩽60 mmHg (diastolic))/CURB-65 (confusion, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) or ⩽60 mmHg (diastolic), age ⩾65 years) [48] and the Revised American Thoracic Society tool [49], were derived to differentiate inpatient from outpatient therapy [50]. Tools to detect early bacteraemia are evolving as the risk for death increased three-fold in this patient population [51]. Specific scores for the assessment of pneumonia are further discussed in chapter 7 [52].

Table 2. Therapeutic strategies for the treatment of community-acquired pneumonia (CAP)

Therapeutic and preventive strategies
Pneumonia assessment for need for admission to the ICU
Appropriate guideline-concordant antibiotic therapy
Use of combination antibiotic therapy (coverage for typical and atypical pathogen)
Early initiation of antibiotics (within 6 h of presentation)
Systemic corticosteroid therapy
Lung-protective ventilation strategies with low tidal volumes
CAP measures/process measures
Immunisation (influenza or pneumococcal infection)

ICU: intensive care unit. Reproduced and modified from [28] with permission from the publisher.

Risk stratification in CAP sepsis

Tools to specifically predict the severity and mortality of many diseases causing multiorgan damage and failure include Acute Physiology and Chronic Health Evaluation (APACHE) II [53], APACHE III [54], the McCabe classification [55], PIRO [56] and SOFA (sequential organ failure assessment) [57]. These scores, originally designed for ICU patients,

can serve as objective parameters for early assessment of illness severity and to compare illness severity across subgroups. Chapter 7 [52] discusses risk assessment scores for pneumonia.

Table 3. Mortality by hospital location and risk stratification

	Mortality %
Hospital location	
Emergency department	27.6
Intensive care unit	41.3
General practice unit	46.8
Haemodynamic classification (suspected infection)	
Pre-hospital lactate >3.5 mmol·L^{-1} [44]	47
Pre-hospital lactate >3.5 mmol·L^{-1} and SBP <100 mmHg [44]	55
Hypotension and vasopressors	36.7
Lactate >4 mmol·L^{-1} only	30.0
Lactate >4 mmol·L^{-1} and SBP <90 mmHg	46.1

SBP: systolic blood pressure. Reproduced from [6] with permission from the publisher.

The resuscitation bundle

The principles of early sepsis management include early identification of high-risk patients, appropriate cultures, source control and appropriate antibiotic administration. This is followed by early haemodynamic optimisation of DO_2 guided by preload (fluid administration guided by central venous pressure (CVP) or a surrogate measure), afterload (vasopressor use based on mean arterial pressure (MAP)), arterial oxygen content (CaO_2) (packed red blood cell (RBC) transfusion for low $ScvO_2$) and contractility (augmentation by inotropes for a persistently low $ScvO_2$). Measures to decrease systemic oxygen demands are the early introduction of sedation, muscle relaxation and mechanical ventilation. In 2001, these interventions, which were also recommended by a consensus of expert opinion [22], were applied at the most proximal site of hospital presentation (fig. 5) [21].

Sepsis is defined as the presence of infection (suspected or confirmed) in combination with systemic manifestations of infection (two or more SIRS (systemic inflammatory response syndrome) criteria). Severe sepsis and septic shock are defined by organ dysfunction or tissue hypoperfusion caused by sepsis (table 4) [58]. To expedite early intervention, the presence of hypotension (systolic blood pressure <90 mmHg) (after a 30-cm^3·kg^{-1} fluid challenge) or a normal blood pressure and a lactate level $\geqslant$4 mmol·L^{-1} identifies CAP patients at high risk of mortality (table 3) [6, 44, 59–61].

Cultures, antibiotics and source control

Obtaining cultures and the administration of appropriate antimicrobials within the first hour of the recognition of septic shock not only decreases mortality but also reduces hospital length of stay (LOS) and costs [62, 63]. Specific antimicrobial treatments are discussed in depth in chapters 11 [64] and 15 [65] for complicated CAP.

The resuscitation of the CAP patient in severe sepsis and septic shock

The principles of shock management should be applied early to patients with severe sepsis and septic shock with CAP. These principles should be structured around the ABCDEs of shock resuscitation to assure delivery of oxygen to tissues to meet metabolic demands: airway; breathing; circulation; delivery of oxygen and demands; while meeting end-points.

A and B: airway and breathing

Intubation and mechanical ventilation

The delivery of oxygen is paramount and begins with either supplemental oxygen, or noninvasive or invasive positive pressure mechanical ventilation (PPMV). The indications are multifactorial, such

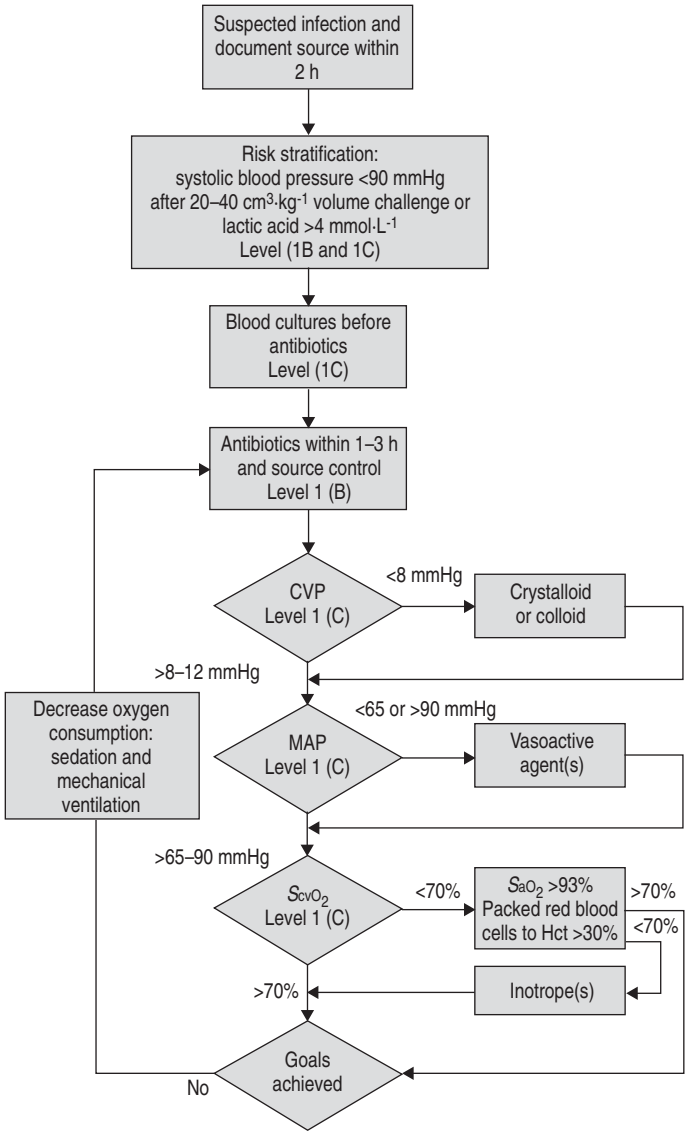

Figure 5. Early goal-directed resuscitation bundle for patients with severe sepsis and septic shock. CVP: central venous pressure; MAP: mean arterial pressure; $S_{cv}O_2$: central venous oxygen saturation; S_aO_2: arterial oxygen saturation; Hct: haematocrit. Reproduced and modified from [21] with permission from the publisher.

as hypoxia, hypercarbia, severe metabolic acidosis, altered mental status, a persistently low $S_{cv}O_2$ [66, 67]: "the look of impending demise". After assuming control of ventilation, acid–base abnormalities can be reversed and, furthermore, the work of breathing, which consumes 20–40% of systemic D_O2, can be eliminated [68, 69]. Noninvasive ventilation (NIV) may be attempted in the absence of severe hypoxia or bilateral alveolar infiltrates; however, prolonged NIV is associated with worse outcomes [13, 70, 71]. Ventilation strategies in CAP are discussed in depth in chapter 13 [72].

The introduction of PPMV can decrease venous return and increase right ventricular distention (as a result of increased pulmonary vascular resistance), which decreases left ventricular filling and cardiac output (fig. 6). Furthermore, the agents that are used for rapid sequence induction can decrease arterial–venous dilation and sympathetic drive, resulting in hypotension. Several studies have shown that up to 25–30% of critically ill patients will develop hypotension following intubation and NIV [73]. To address hypotension, the patient should be volume loaded (30 $cm^3 \cdot kg^{-1}$) and an arterial line should be placed if possible. A vasopressor should be readily available. A bolus-type vasopressor (1 mg of phenylephrine in 10 cm^3 or 1000 μg) can be quickly prepared and given in intravenous boluses of 50 μg. Protective lung strategies improve outcome; however, results for specific ventilator modes remain inconclusive, except for prone positioning [74–76].

Decreasing systemic $V'O_2$

Short-term decreases in $S_{cv}O_2$ are associated with a higher frequency of acute cardiopulmonary events by concealing a mismatch of oxygen supply and demand [67, 77]. Thus, early monitoring will detect high-risk patients for interventions. Normalisation of $S_{cv}O_2$ remains significantly predictive of outcome 47 h after the onset of acute lung injury (ALI) and up to 48 h in the ICU phase of sepsis [78, 79]. In patients with severe adult respiratory distress syndrome, early administration of sedation of muscle relaxation improves outcome and decreases the duration of

Table 4. Severe sepsis and septic shock criteria

Infection, documented or suspected, and some of the following

- General variables
  - Temperature (hypothermia with core temperature <36°C or fever (>38.3°C))
  - Tachycardia (heart rate >90 beats·min^{-1} or more than two SD above the normal value for age)
  - Tachypnoea
  - Altered mental status
  - Significant oedema or positive fluid balance (>20 mL·kg^{-1} over 24 h)
  - Hyperglycaemia (plasma glucose >140 mg·dL^{-1} or 7.7 mmol·L^{-1}) in the absence of diabetes
- Inflammatory variables
  - Leukocytosis (WBC count >12 000 cells·μL^{-1})
  - Leukopenia (WBC count ⩽4000 cells·μL^{-1})
  - Normal WBC count with >10% immature forms (bands)
  - Plasma C-reactive protein >2 SD above the normal value
  - Plasma procalcitonin >2 SD above the normal value
- Haemodynamic variables
  - Arterial hypotension (SBP<90 mmHg, MAP <70 mmHg, or an SBP decrease >40 mmHg in adults or <2 SD below the normal for age)
- Organ dysfunction variables
  - Arterial hypoxaemia (P_{aO_2}/F_{IO_2} <300)
  - Acute oliguria (urine output <0.5 mL·kg^{-1}·h^{-1} for ⩾2 h despite adequate fluid resuscitation)
  - Creatinine increase >0.5 mg·dL^{-1} or 44.2 μmol·L^{-1}
  - Coagulation abnormalities (INR >1.5 or a PTT >60 s)
  - Ileus (absent bowel sounds)
  - Thrombocytopenia (platelet count <100 000 cells·μL^{-1})
  - Hyperbilirubinaemia (plasma total bilirubin >4 mg·dL^{-1} or 70 μmol·L^{-1})
- Tissue perfusion variables
  - Hyperlactaemia (>1 mmol·L^{-1})
  - Decreased capillary refill or mottling

WBC: white blood cell; SBP: systolic blood pressure; MAP: mean arterial pressure; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; INR: international normalised ratio; PTT: partial thromboplastin time. Reproduced and modified from [58] with permission from the publisher.

mechanical ventilation [80, 81]. The outcome benefit may be related to early restoration of the balance between D_{O_2} and V'_{O_2} (fig. 7).

C: circulation

Preload optimisation

Methods used to assess the volume status or cardiac preload include blood pressure (stroke volume or pulse pressure variation (PPV)), heart rate, urine output, CVP and pulmonary artery occlusion pressure (PAOP), or ultrasound assessment of the inferior vena cava (IVC).

When sepsis-induced tissue hypoperfusion persists after the initial fluid challenge of 30 mL·kg^{-1} bodyweight with signs of hypotension (table 5) and/or a blood lactate concentration of more than 4 mmol·L^{-1}, resuscitation efforts should target the more invasive measures to achieve a CVP between 8 and 15 mmHg (spontaneous breathing) or 12 and 15 mmHg (mechanical ventilation), MAP of ⩾65 mmHg, urine output of ⩾0.5 mL·kg^{-1}·h^{-1}, and S_{cvO_2} or S_{vO_2} of 70% or 65%, respectively. These goals should be achieved within the first 6 h after the patient has been identified [58].

CVP is clinically equal to the volume assessments *via* pulmonary artery catheter in the fluid management of ALI [83]. While the discussion regarding the use of CVP for volume assessment continues, the use of CVP in early management of sepsis has been shown to be associated with a reduction in mortality [58, 79, 84–87].

Ultrasound has been proposed as a noninvasive means of measuring volume status and cardiac preload (fig. 8). This has been through the use of IVC measurements for both absolute diameter

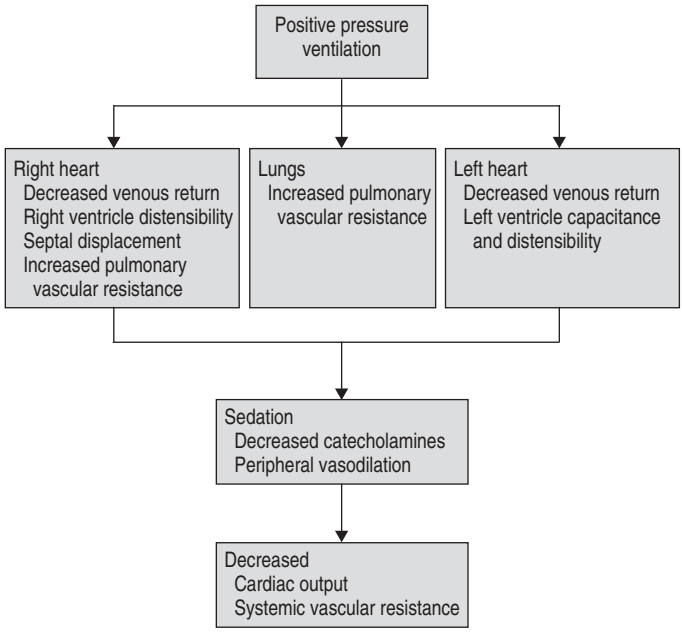

Figure 6. Haemodynamic effects of mechanical ventilation.

and respiratory variation of IVC diameter using a subxiphoid approach. Echocardiography can be used to estimate left ventricular end-diastolic volume (LVEDV), but this approach is dependent on the skill and training of the sonographer [88]. Isolated measurements of LVEDV fail to predict the haemodynamic response to alterations in preload [89]. Intracardiac and vena cava diameters, and LVEDV area measurements after a fluid challenge or passive leg raising may be used to assess volume status. Ultrasound is useful to assist in line placement and cardiac output measurement [90], and to detect myocardial dysfunction, pericardial disease, aortic disease, intraperitoneal fluid and pneumothorax [91, 92].

PPV or stroke volume variation (SVV) during a positive pressure breath in the intubated patient can be used to predict the responsiveness of cardiac output to changes in preload [93]. SVV is defined as the difference between the maximal pulse pressure and the minimum pulse pressure divided by the average of these two pressures [93]. In ventilated patients, measures of SVV using arterial pulse contour analysis estimates cardiac output and can demonstrate fluid responsiveness. A SVV of 13% is highly sensitive and specific for detecting preload responsiveness [94]. SVV has been compared to CVP, PAOP and systolic pressure variation as predictors of preload responsiveness. Patients are classified as preload responsive if their cardiac index increased by at least 10–15% after rapid infusion of a standard volume of intravenous fluid or passive leg raising [93]. Receiver operator curve characteristics demonstrated that SVV was the best predictor of preload responsiveness.

Atrial arrhythmias and spontaneous breathing can interfere with the usefulness of this technique [89]. SVV in mechanically ventilated patients remains a useful approach for assessing preload responsiveness [89]. Other methodologies include trans-oesophageal Doppler, thoracic cutaneous bioimpedance, lithium dilution or transpulmonary thermodilution [95].

Early aggressive fluid therapy is associated with improved outcomes and must be distinguished from late aggressive fluid therapy [96]. The administered volume in the EGDT group within the first 6 h was significantly greater than that of the standard therapy group, but over 72 h, there were no differences in the amount of fluid between the two groups. This is associated with a reduction in vasopressor and, thus, corticosteroid therapy [22, 33, 97, 98].

The choice of resuscitation fluid depends on various clinical factors such as electrolyte imbalances, haemoglobin levels and the logistic availability of specific resuscitation fluids [99].

Afterload optimisation

There is a significant association between the duration of hypotension and outcome in early sepsis, giving rise to the Surviving Sepsis Campaign guidelines SSCGL for a MAP target of $\geqslant$65 mmHg (fig. 5) [83, 100–104]. Selection of the vasopressor takes into consideration the patient's heart rate (table 6). Tachycardia not only increases myocardial oxygen consumption, it decreases stroke volume and efficient cardiac output. While there is no outcome benefit of noradrenaline over dopamine in septic shock, the incidence of tachycardia and arrhythmias associated with dopamine

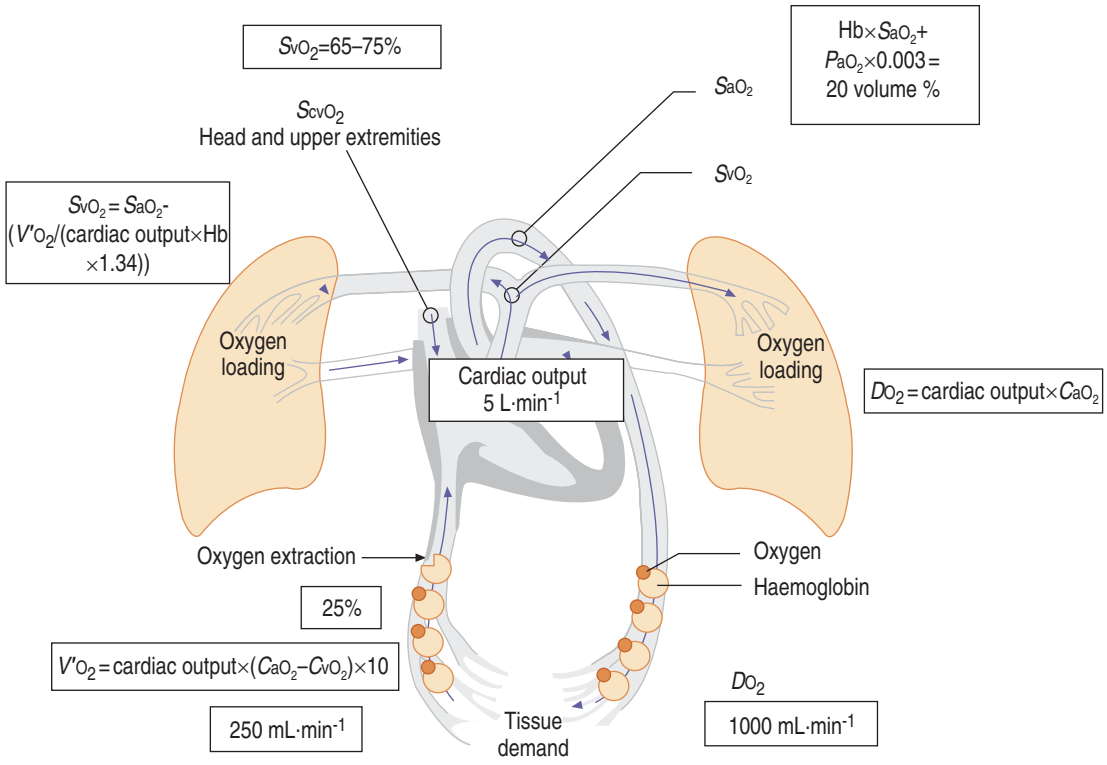

Figure 7. Haemodynamic parameters and formulae. S_{aO_2}: arterial oxygen saturation; Hb: haemoglobin concentration; P_{aO_2}: arterial oxygen tension; S_{vO_2}: venous oxygen saturation; D_{O_2}: oxygen delivery; C_{aO_2}: arterial oxygen content; V'_{O_2}: oxygen consumption; C_{vO_2}: venous oxygen content; S_{cvO_2}: central venous oxygen saturation.

may contribute to its increased mortality in cardiogenic or septic shock [101]. In the case of tachycardia (heart rate >120 beats·min^{-1}), a stronger α-agonist (phenylephrine) may be indicated. There is evidence that radial artery pressure monitoring underestimates central arterial (femoral) pressure when using high-dose vasopressor therapy [101, 106]. Low-dose vasopressin has not been shown to improve outcome [101].

One of the benefits of aggressive fluid therapy is a 15% reduction in vasopressor use during the first 6 h. This early reduction in vasopressor therapy further reduces the need for controversial therapies such as vasopressin and corticosteroid therapy [33, 97]. Vasopressor therapy may falsely increase CVP and mask hypovolaemia [107]. Hypotension is more refractory to fluid administration at the later stages of disease and is associated with increased morality [33].

Steroid therapy in septic shock

Rationales for steroid treatment in septic shock are based on their anti-inflammatory properties and effect on the vascular tone. The SSCGL recommend that steroids should not be given unless the patient is adequately volume resuscitated [108]. If, after the initial resuscitation, the patient remains haemodynamically unstable, requiring vasopressor support, the use of intravenous hydrocortisone is suggested, regardless of the results of an adrenocorticotrophic hormone stimulation test [109]. For patients with severe CAP, risk assessment should take into consideration patients with severe chronic obstructive pulmonary disease and asthma that may have received intermittent treatment with steroids before their septic episode, and, therefore, have iatrogenic adrenal insufficiency, needing steroid replacement [45]. The initiated treatment should be quickly tapered when no longer required.

Table 5. Common resuscitation fluids

	Albumin		Dextran		Gelatine	Crystalloid	
	4%, 5%	20–25%	10% dextran-40	3% dextran-60, 6% dextran-70	Succinylated and cross-linked 2.5%, 3%, 4%; urea-linked 3.5%	Normal saline	LR
Molecular weight kDa	69	69	40	70	30–35	0	0
Osmolality $mOsm \cdot L^{-1}$	290	310	280–324	280–324	300–350	285–308	250–273
Colloid osmotic pressure mmHg	20–30	70–100	20–60	20–60	25–42	0	0
Maximum volume expansion % administered volume	70–100	300–500	100–200	80–140	70–80	25–25	20–25
Duration of volume expansion h	12–24	12–24	1–2	⩽8–24	⩽4–6	1–4	1–4
Plasmatic half-life h	16–24	16–24	4–6	~12	~2–9	0.5	0.5
Potential adverse reactions	+	+	+++	+++	+	+	+
Side-effects described	Allergic reaction Transmitted infection	Allergic reaction Transmitted infection	Anaphylactoid reactions Allergic reaction Interference with blood cross-matching	Anaphylactoid reactions Allergic reaction Interference with blood cross-matching	High calcium content (urea-linked forms) Anaphylactoid reactions	Hyperchloraemic metabolic acidosis	Hyperkalaemia

Table 5. Continued

	Albumin		Dextran		Gelatine	Crystalloid	
	4%, 5%	20–25%	10% dextran-40	3% dextran-60, 6% dextran-70	Succinylated and cross-linked 2.5%, 3%, 4%; urea-linked 3.5%	Normal saline	LR
Comments	Albumin is a protein derived from human plasma The SAFE trial compared the effect of fluid resuscitation with albumin or saline on mortality and found similar 28-day mortalities and secondary outcomes in each arm A subset of patients with sepsis and ALI resuscitated with albumin showed a nonsignificant decrease in mortality		Dextrans are not frequently used for rapid plasma expansion, but rather to lower blood viscosity This class can cause renal dysfunction, as well as anaphylactoid reactions		Gelatines (*e.g.* Haemaccel[#]) are produced from bovine collagen Because they have a much smaller molecular weight, they are not as effective in expanding plasma volume; however, they cost less Gelatines have been reported to cause renal impairment, as well as allergic reactions ranging from pruritus to anaphylaxis These substances are currently not used in North America Because of the significant calcium content in these products, blood should not be transfused through tubing previously used for this product	Slightly hyperosmolar solution containing 154 mEq·L^{1-} of both sodium and chloride Due to the relative high chloride concentration, normal saline carries the risk of inducing hyperchloraemic metabolic acidosis when given in large amounts	LR results in a buffering of the acidaemia, which is advantageous over normal saline Due to the fact that LR contains potassium, albeit a very small amount, there is a small risk of inducing hyperkalaemia in patients with renal insufficiency or renal failure There is a theoretical issue of using LR because of significant immune activation and induction of cellular injury caused by the D-isomer of LR

LR: lactated Ringer's solution; +: mild; +++: severe; SAFE: Saline *versus* Albumin Fluid Evaluation; ALI: acute lung injury. [#]: Piramal Healthcare Ltd, Mumbai, India. Reproduced and modified from [82] with permission from the publisher.

ANNANE *et al.* [110] recommended a moderate dose of corticosteroids especially in severe CAP with a high predicted mortality, such as patients in respiratory failure or shock and patients with progression to organ dysfunction despite antibiotic treatment. The rationale behind this recommendation was the observation that, in patients with acute respiratory distress syndrome (ARDS), a deficient glucocorticoid-mediated downregulation of inflammatory cytokine and chemokine transcription occurred despite elevated levels of circulating cortisol. Pneumonia was the precipitating insult in many patients with ARDS. Downregulation of systemic inflammation is essential to restoring homeostasis, decreasing morbidity and improving survival [111].

Early treatment with hydrocortisone in patients with severe CAP prevented the progression of these patients to septic shock and ARDS. In patients with signs of early ARDS, treatment with methylprednisolone prevented progression to respiratory failure and the need for mechanical ventilation [112]. MEIJIVIS *et al.* [113] replicated these findings for immunocompetent patients receiving antibiotic therapy, resulting in a reduction in length of hospital stay. However, as stated [110], the recommendation should be applied only to the most severe cases of CAP. SNIJDERS *et al.* [114] found that daily treatment with prednisone 40 mg for 1 week in patients hospitalised with CAP did not improve outcomes and was associated with late treatment failure, and cautioned about the routine use of prednisolone in the treatment of CAP.

D: delivery

Optimising D_{O_2}

The immediate goal in resuscitation is to ensure enough D_{O_2} to meet metabolic demands. Many of the salutary effects of S_{cvO_2} monitoring are based on its ability to detect early imbalances of D_{O_2} and V'_{O_2} [115, 116]. S_{cvO_2} is a trigger for increasing inspired oxygen concentration to improve arterial hypoxia, RBC transfusion to increase C_{aO_2}, inotropic therapy to improve cardiac output and oxygen delivery, and mechanical ventilation to decrease systemic oxygen demand [66, 117, 118]. Multiple studies including meta-analysis have shown that attaining a target S_{cvO_2} with the first 6 h of resuscitation significantly impacts mortality [119–121]. S_{cvO_2} is significantly predictive of outcome 47 h after the onset of ALI and up to 48 h in the ICU phase of sepsis [78, 79]. Further evidence exists showing that continuous S_{cvO_2} monitoring is superior to intermittent monitoring [122].

Arterial oxygen concentration

Hypoxaemia has been shown to have a strong association with the diagnosis of CAP [123]. Survival in severe CAP is associated with improvements in the arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) ratio [124]. The P_{aO_2}/F_{IO_2} ratio is an essential factor in the classification of lung injury. As mentioned before, this may include the need for mechanical ventilation.

Haemoglobin

Anaemia results from a combination of pre-existing disease, acute volume resuscitation, impaired marrow response and a proposed decrease in the sensitivity of erythropoietin receptors [125]. Thus, septic patients lack the compensatory ability to increase haemoglobin concentrations acutely from the bone marrow. Current recommendations target a haemoglobin level of 7–9 $g \cdot dL^{-1}$ [58]. Anaemia triggers a compensatory increase in systemic oxygen extraction. If there is not a compensatory increase in cardiac output, global tissue hypoxia ensues [126]. Transfusion of RBCs during this uncompensated, delivery-dependent state (increased lactate and low S_{cvO_2}) is warranted [21, 37]. This concept has been supported by VALLET *et al.* [117], who found that mortality is optimised when an S_{cvO_2} of 69.5% is used as a trigger for transfusion.

RBC storage time has been shown to have no influence on the microvascular response to RBC transfusion. The sublingual microcirculation is globally unaltered by RBC transfusion in septic patients; however, it can improve in patients with altered capillary perfusion at baseline [127]. While several studies have demonstrated an association between RBC transfusions and worse outcomes in critically ill patients [128], observational studies conclude that blood transfusions are

not associated with increased mortality [129, 130]. Neither haemoglobin nor haematocrit accurately reflect total body red cell mass, which makes targeting an optimal number an issue of continued debate [131]. Further studies are needed to support current expert opinion recommendations to maintain a haemoglobin concentration of 10 $mg \cdot dL^{-1}$ during early septic shock [105].

Myocardial dysfunction

Myocardial dysfunction is present in up to 15% of patients with severe sepsis and septic shock [132] but is frequently not evident on physical examination [78]. Multiple studies have shown that recognition and treatment of early myocardial dysfunction is associated with decreased mortality [133]. An elevated brain natriuretic peptide concentration (>230 $pg \cdot mL^{-1}$) is significantly associated with myocardial dysfunction and severity of global tissue hypoxia [134]. A low $S_{cv}O_2$ despite adequate resuscitation and optimisation of DO_2 implies myocardial dysfunction [118].

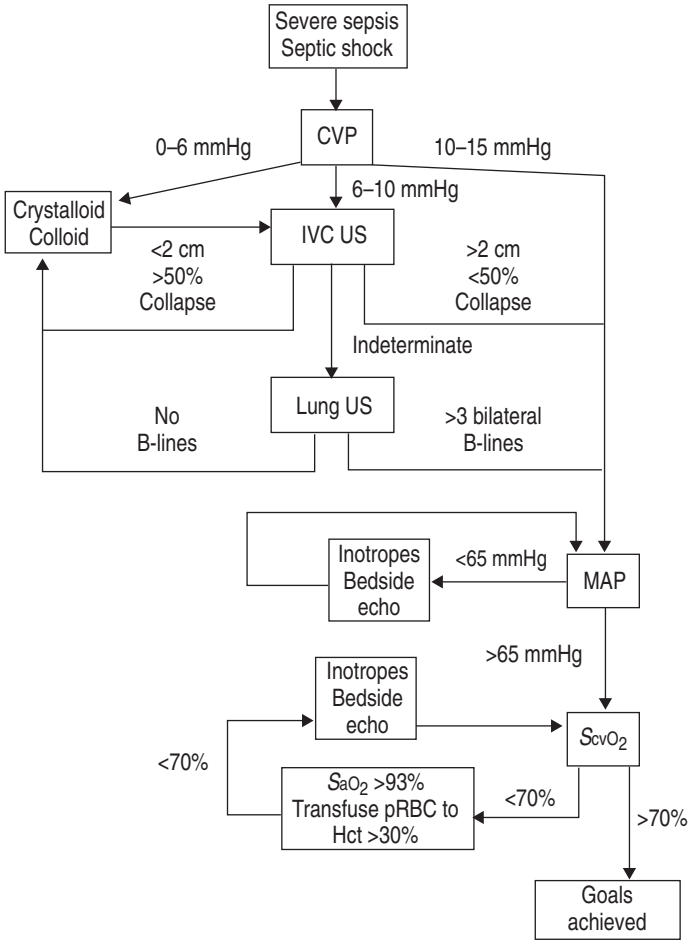

Figure 8. Ultrasound (US) to augment resuscitation efforts. CVP: central venous pressure; IVC: inferior vena cava; MAP: mean arterial pressure; echo: echocardiography; $S_{cv}O_2$: central venous oxygen saturation; S_aO_2: arterial oxygen saturation; pRBC: packed red blood cells; Hct: haematocrit.

Dobutamine is the most frequently used agent but may cause hypotension, tachycardia and tachyarrthymias. In the presence of tachycardia, digoxin may be helpful adjunct. NASRAWAY *et al.* [135] demonstrated that 20 septic patients treated with digoxin had a significant increase in left ventricular stroke work over dopamine-treated patients ($13 \pm 10\%$ compared with $74 \pm 16\%$, $p<0.02$).

The development of atrial fibrillation is a significant haemodynamic event. In a recent observational study in 49 082 patients presenting with sepsis, the incidence of new-onset atrial fibrillation was 5.9%. These patients also had a 4.3 times higher incidence of stroke (2.6%) and 1.4 times higher in-hospital mortality (56%) compared with those with no atrial fibrillation or pre-existing atrial fibrillation. There is no current outcome evidence on whether aggressive pharmacological therapy or cardioversion is beneficial in this setting [136].

E: end-points

The role of lactate clearance

NGUYEN and co-workers [137, 138] retrospectively found that the clearance of lactate ((initial lactate-final lactate)/initial lactate) over the first 6 h after presentation was associated with a significant decrease in pro- and anti-inflammatory biomarkers, improved organ function, and reduced mortality. This was based on previous investigations using lactate clearance over varying time periods of 24, 48 and 72 h in the ICU setting [139].

Table 6. Vasopressors and inotropes

Agent	Dose range	Vaso-constriction	Vaso-dilation	Heart rate	Contractility	Dysrhythmias	Typical use
Dopamine	1–4 μg·kg^{-1}·min^{-1}	0	1+	1+	1+	1+	''Renal dose'', does not improve renal function May be used with bradycardia and hypotension
	5–10 μg·kg^{-1}·min^{-1}	1–2+	1+	2+	2+	2+	Can be used as an inotrope in this range
	11–20 μg·kg^{-1}·min^{-1}	2–3+	1+	2+	2+	3+	Vasopressor range Best for patients with no tachycardia
Vasopressin	0.04–0.1 U·min^{-1}	3–4+	0	0	0	1+	Can be used when tachycardia is present No outcome benefit [105]
Phenylephrine	20–200 μg·min^{-1}	4+	0	0	0	1+	Best with tachycardia
Noradrenaline	2–20 μg·min^{-1}	4+	0	2+	2+	2+	Consider as first line for septic shock
Adrenaline	1–20 μg·min^{-1}	4+	0	4+	4+	4+	Refractory shock
Dobutamine	1–20 μg·kg^{-1}·min^{-1}	1+	2+	1–2+	3+	3+	Myocardial suppression

Using a noninferiority research design, JONES *et al.* [140] investigated whether a lactate clearance of 10% is equivalent to reaching the $S_{cv}O_2$ goal in the EGDT protocol. Compared with the EGDT study, the patients enrolled by JONES *et al.* [140] were of a lower illness severity, in a more supply-independent phase at baseline (normal $S_{cv}O_2$ and lower lactate levels), more frequently in vasodilatory shock (vasopressor dependent) and less often mechanically ventilated. More importantly, only 30 interventions were made involving 10% of the patient population. Because of that lack of interventions, JONES *et al.* [140] failed to address delivery-dependent or hypodynamic patients who may benefit from supplemental oxygen, packed RBCs, inotropes and mechanical ventilation to optimise D_{O_2} (online supplementary fig. 2). $S_{cv}O_2$ decreases before lactate levels increase, so providing these pre-emptive therapies may contribute to a reduction in sudden cardiopulmonary complications within the first 72 h of disease onset [21].

20–50% of septic shock patients will never develop elevated lactate levels. These patients frequently develop multisystem organ failure [26, 141]. Given this information, an elevated lactate concentration is helpful to identify high-risk patients and can be used to monitor the adequacy of resuscitation. Lactate and $S_{cv}O_2$ are complimentary resuscitation end-points and are not mutually exclusive [142].

Adjuvant possible treatments

Selenium therapy has been shown to reduce mortality in sepsis. A recent meta-analysis of randomised controlled trials found that selenium supplementation at higher than daily doses

reduced sepsis mortality; however, there was no effect on hospital LOS or the occurrence of nosocomial infections [143].

In Japan, thrombomodulin is used in patients with severe sepsis, septic shock and a coagulopathy. This intervention uses a similar pathway to activated protein C [144]. Clinical trials for a wider application of thrombomodulin in patients with severe sepsis and septic shock in Europe and North America are currently underway.

In Gram-negative sepsis, which can also accompany a pulmonary source, especially in the elderly patients [9], polymyxin haemoperfusion has been used in Japan for more than two decades. Experience from the Italian EUPHAS (Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock) trial has shown a mortality reduction [145]. However, this treatment is limited to patients with suspected Gram-negative septic shock.

Targeted sepsis therapy (interleukin (IL)-1, IL-6, IL-8 and tumour necrosis factor-α) has failed, as patients may have been enrolled too late. Additionally, there is a growing body of evidence that targeted immunomodulatory therapy for sepsis treatment should not target a single cytokine but, possibly, a distinct panel of cytokines at various patient-dependent time-points similar to cancer treatment [146].

Outcomes

Over the last 8 years, the in-hospital mortality of severe sepsis declined steadily, from 39.6% to 27.3%, and that of septic shock from 47.1% to 36.4% [4]. Over the same period, hospital admissions for sepsis have increased over 100% (from 11.6 per 10 000 to 24.0 per 10 000). Again over this same time period, the outcome benefit of the original EGDT study has been robustly replicated in over 50 studies involving over 30 000 patients [25] in both the emergency department and ICU settings [26, 147, 148], and in the community and tertiary hospital settings [149, 150]. Coba *et al.* [151] and Castellano-Ortega *et al.* [152] assessed compliance to all resuscitation bundle goals at 6, 18 and 24 h after diagnosis. EGDT was found to be effective up to 18 h after meeting criteria for the resuscitation bundle [151, 152].

The hospital admission for sepsis is the most expensive admission and is responsible for 11% of hospital costs (over $64 billion per year) in the USA. It is estimated that a 4–5-day reduction in hospital LOS and a 20% overall reduction in these hospital-related costs have been realised with the resuscitation bundle [25, 26].

Conclusions

CAP is an infection that is a frequent cause of severe sepsis and septic shock. It is a deadly and expensive cause of hospitalisation worldwide. When treating a patient with CAP, it is important for the clinician to equate this with sepsis and adequately risk stratify to an illness severity that requires the level of intervention that is associated with the best outcomes. This level of intervention is the ABCDE approach, which leads to reduced morbidity and mortality, LOS and economic costs. In following these recommendations, an additional one out of every five to six patients presenting with this illness severity will survive to hospital discharge.

Statement of Interest
None declared.

References

1. Moss M. Epidemiology of sepsis: race, sex, and chronic alcohol abuse. *Clin Infect Dis* 2005; 41: Suppl. 7, S490–S497.
2. Daniels R. Surviving the first hours in sepsis: getting the basics right (an intensivist's perspective). *J Antimicrob Chemother* 2011; 66: Suppl. 2, ii11–ii23.

3. Reed K, May R, Nicholas C, *et al.* HealthGrades Patient Safety in American Hospitals Study March 2011 www.cpmhealthgrades.com/CPM/assets/File/HealthGradesPatientSafetyInAmericanHospitalsStudy2011.pdf
4. Kumar G, Kumar N, Taneja A, *et al.* Nationwide trends of severe sepsis in the 21st century (2000–2007). *Chest* 2011; 140: 1223–1231.
5. Hall MJ, Williams SN, De Frances CJ, *et al.* Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. *NCHS Data Brief* 2011; 62: 1–8.
6. Levy MM, Dellinger RP, Townsend SR, *et al.* The surviving sepsis campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Intensive Care Med* 2010; 36: 222–231.
7. Gaieski DF, Mikkelsen ME, Band RA, *et al.* Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med* 2010; 38: 1045–1053.
8. Levy MM, Artigas A, Phillips GS, *et al.* Outcomes of the surviving sepsis campaign in intensive care units in the USA and Europe: a prospective cohort study. *Lancet Infect Dis* 2012; 12: 919–924.
9. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. *Crit Care Med* 2006; 34: 15–21.
10. Anderson JL, Adams CD, Antman EM, *et al.* 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011; 123: e426–e579.
11. Jauch EC, Cucchiara B, Adeoye O, *et al.* Part 11: adult stroke: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; 122: Suppl. 3, S818–S828.
12. Centers for Disease Control and Prevention. Number and rate of discharges from short-stay hospitals and of days of care, with average length of stay and standard error, by selected first-listed diagnostic categories: United States, 2010. www.cdc.gov/nchs/data/nhds/2average/2010ave2_firstlist.pdf Date last accessed: 2013. Date last updated: 2010.
13. Aliberti S, Amir A, Peyrani P, *et al.* Incidence, etiology, timing, and risk factors for clinical failure in hospitalized patients with community-acquired pneumonia. *Chest* 2008; 134: 955–962.
14. Restrepo MI, Mortensen EM, Velez JA, *et al.* A comparative study of community-acquired pneumonia patients admitted to the ward and the ICU. *Chest* 2008; 133: 610–617.
15. Lagu T, Rothberg MB, Shieh MS, *et al.* Hospitalizations, costs, and outcomes of severe sepsis in the united states 2003 to 2007. *Crit Care Med* 2012; 40: 754–761.
16. Lemay AC, Anzueto A, Restrepo MI, *et al.* Predictors of long-term mortality after severe sepsis in the elderly. *Am J Med Sci* 2013 [In press DOI: 10.1097/MAJ.0b013e318295a147].
17. Wichmann MW, Inthorn D, Andress HJ, *et al.* Incidence and mortality of severe sepsis in surgical intensive care patients: the influence of patient gender on disease process and outcome. *Intensive Care Med* 2000; 26: 167–172.
18. de Montmollin E, Tandjaoui-Lambiotte Y, Legrand M, *et al.* Outcomes in critically ill cancer patients with septic shock of pulmonary origin. *Shock* 2013; 39: 250–254.
19. Nathens AB, Jurkovich GJ, Maier RV, *et al.* Relationship between trauma center volume and outcomes. *JAMA* 2001; 285: 1164–1171.
20. Marshall JC, al Naqbi A. Principles of source control in the management of sepsis. *Crit Care Clin*, 25: 753–768.
21. Rivers E, Nguyen B, Havstad S, *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345: 1368–1377.
22. Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine. *Crit Care Med* 1999; 27: 639–660.
23. Rivers EP, Kruse JA, Jacobsen G, *et al.* The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock. *Crit Care Med* 2007; 35: 2016–2024.
24. Kiers HD, Griesdale DE, Litchfield A, *et al.* Effect of early achievement of physiologic resuscitation goals in septic patients admitted from the ward on the kidneys. *J Crit Care* 2010; 25: 563–569.
25. Rivers EP, Katranji M, Jaehne KA, *et al.* Early interventions in severe sepsis and septic shock: a review of the evidence one decade later. *Minerva Anestesiol* 2012; 78: 712–724.
26. Cannon CM, Holthaus CV, Zubrow MT, *et al.* The GENESIS project (GENeralized Early Sepsis Intervention Strategies): a multicenter quality improvement collaborative. *J Intensive Care Med* 2013; 28: 355–368.
27. Fernandez JF, Sibila O, Restrepo MI. Predicting ICU admission in community-acquired pneumonia: clinical scores and biomarkers. *Expert Rev Clin Pharmacol* 2012; 5: 445–458.
28. Restrepo MI, Anzueto A. Severe community-acquired pneumonia. *Infect Dis Clin North Am* 2009; 23: 503–520.
29. DeFrances CJ, Cullen KA, Kozak LJ. National Hospital Discharge Survey: 2005 annual summary with detailed diagnosis and procedure data. *Vital Health Stat 13* 2007; 165: 1–209.
30. Mondrinos MJ, Kennedy PA, Lyons M, *et al.* Protein kinase C and acute respiratory distress syndrome. *Shock* 2013; 39: 467–479.
31. Rackow EC, Astiz ME. Pathophysiology and treatment of septic shock. *JAMA* 1991; 266: 548–554.
32. Brun-Buisson C, Doyon F, Carlet J, *et al.* Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU group for severe sepsis. *JAMA* 1995; 274: 968–974.

33. Levy MM, Macias WL, Vincent JL, *et al.* Early changes in organ function predict eventual survival in severe sepsis. *Crit Care Med* 2005; 33: 2194–2201.
34. Bronicki RA. Venous oximetry and the assessment of oxygen transport balance. *Pediatr Crit Care Med* 2011; 12: Suppl., S21–S26.
35. Carr GE, Edelson DP, Yuen TC, *et al.* In-hospital cardiac arrest among patients with coexisting pneumonia: a report from the American Heart Association's Get with the Guidelines – Resuscitation Program. *Am J Respir Crit Care Med* 2011; 183: A6339.
36. Astiz ME, Rackow EC, Weil MH. Oxygen delivery and utilization during rapidly fatal septic shock in rats. *Circ Shock* 1986; 20: 281–290.
37. Rivers EP, Ander DS, Powell D. Central venous oxygen saturation monitoring in the critically ill patient. *Curr Op Crit Care* 2001; 7: 204–211.
38. Friedman G, De Backer D, Shahla M, *et al.* Oxygen supply dependency can characterize septic shock. *Intensive Care Med* 1998; 24: 118–123.
39. Rahal L, Garrido AG, Cruz RJ Jr, *et al.* Fluid replacement with hypertonic or isotonic solutions guided by mixed venous oxygen saturation in experimental hypodynamic sepsis. *J Trauma* 2009; 67: 1205–1212.
40. Ince C. The microcirculation is the motor of sepsis. *Crit Care* 2005; 9: Suppl. 4, S13–S19.
41. Edul VK, Ferrara G, Dubin A. Microcirculatory dysfunction in sepsis. *Endocr Metab Immune Disord Drug Targets* 2010; 10: 235–246.
42. Boulos M, Astiz ME, Barua RS, *et al.* Impaired mitochondrial function induced by serum from septic shock patients is attenuated by inhibition of nitric oxide synthase and poly(ADP-ribose) synthase. *Crit Care Med* 2003; 31: 353–358.
43. Estenssoro E, Gonzalez F, Laffaire E, *et al.* Shock on admission day is the best predictor of prolonged mechanical ventilation in the ICU. *Chest* 2005; 127: 598–603.
44. Jansen TC, van Bommel J, Mulder PG, *et al.* The prognostic value of blood lactate levels relative to that of vital signs in the pre-hospital setting: a pilot study. *Crit Care* 2008; 12: R160.
45. Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44: Suppl. 2, S27–S72.
46. Howell MD, Talmor D, Schuetz P, *et al.* Proof of principle: the predisposition, infection, response, organ failure sepsis staging system. *Crit Care Med* 2011; 39: 322–327.
47. Fine MJ, Auble TE, Yealy DM, *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336: 243–250.
48. British Thoracic Society Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults. *Thorax* 2001; 56: Suppl. 4, iv1–iv64.
49. Ewig S, de Roux A, Bauer T, *et al.* Validation of predictive rules and indices of severity for community acquired pneumonia. *Thorax* 2004; 59: 421–427.
50. Aujesky D, Fine MJ. Community-acquired pneumonia: treatment at home or in the hospital? *Am J Med* 2008; 121: 1038–1040.
51. California Hospital Outcomes Program. Community-acquired pneumonia: hospital outcomes in California, 1999-2001. Sacramento, Office of Statewide Health Planning and Development, 2004; pp. 1–147.
52. Sintes H, Sibila O, Waterer GW, *et al.* Severity assessment tools in CAP. *In:* Chalmers JD, Pletz MW, Aliberti S, eds. Community-Acquired Pneumonia. *Eur Respir Monogr* 2014; 63: 88–104.
53. Knaus WA, Draper EA, Wagner DP, *et al.* APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13: 818–829.
54. Knaus WA, Wagner DP, Draper EA, *et al.* The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991; 100: 1619–1636.
55. McCabe WR JG. Gram-negative bacteremia: I. Etiology and ecology. *Arch Intern Med* 1962; 110: 847–855.
56. de Groot B, Lameijer J, de Deckere ER, *et al.* The prognostic performance of the predisposition, infection, response and organ failure (PIRO) classification in high-risk and low-risk emergency department sepsis populations: comparison with clinical judgement and sepsis category. *Emerg Med J* 2013 [In press DOI: 10.1136/emermed-2012-202165].
57. Vincent JL, Moreno R, Takala J, *et al.* The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22: 707–710.
58. Dellinger RP, Levy MM, Rhodes A, *et al.* Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41: 580–637.
59. Mikkelsen ME, Miltiades AN, Gaieski DF, *et al.* Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med* 2009; 37: 1670–1677.
60. Trzeciak S, Dellinger RP, Chansky ME, *et al.* Serum lactate as a predictor of mortality in patients with infection. *Intensive Care Med* 2007; 33: 970–977.
61. Shapiro NI, Howell MD, Talmor D, *et al.* Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med* 2005; 45: 524–528.
62. Hutchison RW, Govathoti DA, Fehlis K, *et al.* Improving severe sepsis outcomes: Cost and time to first antibiotic dose. *Dimens Crit Care Nurs* 2011; 30: 277–282.

63. Kumar A, Ellis P, Arabi Y, *et al.* Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest* 2009; 136: 1237–1248.
64. Woodhead M, Noor M. Empirical antibiotic management of adult CAP. *In:* Chalmers JD, Pletz MW, Aliberti S, eds. Community-Acquired Pneumonia. *Eur Respir Monogr* 2014; 63: 140–154.
65. Aliberti S, Faverio P. Early outcomes in CAP: clinical stability, clinical failure and nonresolving pneumonia. *In:* Chalmers JD, Pletz MW, Aliberti S, eds. Community-Acquired Pneumonia. *Eur Respir Monogr* 2014; 63: 205–218.
66. Hernandez G, Pena H, Cornejo R, *et al.* Impact of emergency intubation on central venous oxygen saturation in critically ill patients: a multicenter observational study. *Crit Care* 2009; 13: R63.
67. Krafft P, Steltzer H, Hiesmayr M, *et al.* Mixed venous oxygen saturation in critically ill septic shock patients. The role of defined events. *Chest* 1993; 103: 900–906.
68. Hussain SN, Simkus G, Roussos C. Respiratory muscle fatigue: a cause of ventilatory failure in septic shock. *J Appl Physiol* 1985; 58: 2033–2040.
69. Manthous CA, Hall JB, Kushner R, *et al.* The effect of mechanical ventilation on oxygen consumption in critically ill patients. *Am J Respir Crit Care Med* 1995; 151: 210–214.
70. Brochard L, Mancebo J, Wysocki M, *et al.* Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; 333: 817–822.
71. Ferrer M, Esquinas A, Leon M, *et al.* Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. *Am J Respir Crit Care Med* 2003; 168: 1438–1444.
72. Ferrer M. Acute respiratory failure due to CAP. *In:* Chalmers JD, Pletz MW, Aliberti S, eds. Community-Acquired Pneumonia. *Eur Respir Monogr* 2014; 63: 168–183.
73. Manthous CA. Avoiding circulatory complications during endotracheal intubation and initiation of positive pressure ventilation. *J Emerg Med* 2010; 38: 622–631.
74. Amato MB, Barbas CS, Medeiros DM, *et al.* Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338: 347–354.
75. Schadler D, Elke G, Engel C, *et al.* Ventilatory strategies in septic patients. Results from a nationwide observational trial. *Anaesthesist* 2013; 62: 27–33.
76. Guerin C, Reignier J, Richard JC, *et al.* Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368: 2159–2168.
77. Heiselman D, Jones J, Cannon L. Continuous monitoring of mixed venous oxygen saturation in septic shock. *J Clin Monit* 1986; 2: 237–245.
78. Grissom CK, Morris AH, Lanken PN, *et al.* Association of physical examination with pulmonary artery catheter parameters in acute lung injury. *Crit Care Med* 2009; 37: 2720–2726.
79. Varpula M, Tallgren M, Saukkonen K, *et al.* Hemodynamic variables related to outcome in septic shock. *Intensive Care Med* 2005; 31: 1066–1071.
80. Papazian L, Forel JM, Gacouin A, *et al.* Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363: 1107–1116.
81. Steingrub JS, Lagu T, Rothberg MB, *et al.* Treatment with neuromuscular blocking agents and the risk of in-hospital mortality among mechanically ventilated patients with severe sepsis. *Crit Care Med* 2013; 42: 90–96.
82. Rivers EP, Jaehne AK, Eichhorn-Wharry L, *et al.* Fluid therapy in septic shock. *Curr Op Crit Care* 2010; 16: 297–308.
83. Lichtwarck-Aschoff M, Zeravik J, Pfeiffer UJ. Intrathoracic blood volume accurately reflects circulatory volume status in critically ill patients with mechanical ventilation. *Intensive Care Med* 1992; 18: 142–147.
84. Ferrer R, Artigas A, Suarez D, *et al.* Effectiveness of treatments for severe sepsis: a prospective, multicenter, observational study. *Am J Respir Crit Care Med* 2009; 180: 861–866.
85. Boyd JH, Forbes J, Nakada TA, *et al.* Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011; 39: 259–265.
86. Murphy CV, Schramm GE, Doherty JA, *et al.* The importance of fluid management in acute lung injury secondary to septic shock. *Chest* 2009; 136: 102–109.
87. Magder S, Bafaqeeh F. The clinical role of central venous pressure measurements. *J Intensive Care Med* 2007; 22: 44–51.
88. Smith MD, MacPhail B, Harrison MR, *et al.* Value and limitations of transesophageal echocardiography in determination of left ventricular volumes and ejection fraction. *J Am Coll Cardiol* 1992; 19: 1213–1222.
89. Gunn SR, Pinsky MR. Implications of arterial pressure variation in patients in the intensive care unit. *Curr Op Crit Care* 2001; 7: 212–217.
90. Beaulieu Y. Bedside echocardiography in the assessment of the critically ill. *Crit Care Med* 2007; 35: Suppl., S235–S249.
91. Rozycki GS. Surgeon-performed ultrasound: its use in clinical practice. *Ann Surg* 1998; 228: 16–28.
92. Rozycki GS, Ballard RB, Feliciano DV, *et al.* Surgeon-performed ultrasound for the assessment of truncal injuries: lessons learned from 1540 patients. *Ann Surg* 1998; 228: 557–567.
93. Michard F, Chemla D, Richard C, *et al.* Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP. *Am J Respir Crit Care Med* 1999; 159: 935–939.
94. Michard F, Lopes M, Auler JO. Pulse pressure variation: beyond the fluid management of patients with shock. *Crit Care* 2007; 11: 131.
95. Prentice D, Sona C. Esophageal Doppler monitoring for hemodynamic assessment. *Crit Care Nurs Clin North Am* 2006; 18: 189–193.

96. Murphy CV, Schramm GE, Doherty JA, *et al.* The importance of fluid management in acute lung injury secondary to septic shock. *Chest* 2009; 136: 102–109.
97. Cohen R. Use of corticosteroids in septic shock. *Minerva Anestesiol* 2011; 77: 190–195.
98. Micek ST, Roubinian N, Heuring T, *et al.* Before–after study of a standardized hospital order set for the management of septic shock. *Crit Care Med* 2006; 34: 2707–2713.
99. Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med* 2013; 369: 1243–1251.
100. Lanspa MJ, Brown SM, Hirshberg EL, *et al.* Central venous pressure and shock index predict lack of hemodynamic response to volume expansion in septic shock: a prospective, observational study. *J Crit Care* 2012; 27: 609–615.
101. Hollenberg SM. Vasoactive drugs in circulatory shock. *Am J Respir Crit Care Med* 2011; 183: 847–855.
102. Dunser MW, Takala J, Ulmer H, *et al.* Arterial blood pressure during early sepsis and outcome. *Intensive Care Med* 2009; 35: 1225–1233.
103. Jhanji S, Stirling S, Patel N, *et al.* The effect of increasing doses of norepinephrine on tissue oxygenation and microvascular flow in patients with septic shock. *Crit Care Med* 2009; 37: 1961–1966.
104. Thooft A, Favory R, Salgado DR, *et al.* Effects of changes in arterial pressure on organ perfusion during septic shock. *Crit Care* 2011; 15: R222.
105. Hebert PC, Tinmouth A, Corwin HL. Controversies in RBC transfusion in the critically ill. *Chest* 2007; 131: 1583–1590.
106. Dorman T, Breslow MJ, Lipsett PA, *et al.* Radial artery pressure monitoring underestimates central arterial pressure during vasopressor therapy in critically ill surgical patients. *Crit Care Med* 1998; 26: 1646–1649.
107. Nouira S, Elatrous S, Dimassi S, *et al.* Effects of norepinephrine on static and dynamic preload indicators in experimental hemorrhagic shock. *Crit Care Med* 2005; 33: 2339–2343.
108. Dellinger RP, Levy MM, Rhodes A, *et al.* Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; 39: 165–228.
109. Annane D, Sebille V, Charpentier C, *et al.* Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288: 862–871.
110. Annane D, Meduri GU, Marik P. Critical illness-related corticosteroid insufficiency and community-acquired pneumonia: back to the future! *Eur Respir J* 2008; 31: 1150–1152.
111. Meduri GU, Annane D, Chrousos GP, *et al.* Activation and regulation of systemic inflammation in ARDS: rationale for prolonged glucocorticoid therapy. *Chest* 2009; 136: 1631–1643.
112. Confalonieri M, Urbino R, Potena A, *et al.* Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med* 2005; 171: 242–248.
113. Meijvis SC, Hardeman H, Remmelts HH, *et al.* Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; 377: 2023–2030.
114. Snijders D, Daniels JM, de Graaff CS, *et al.* Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. *Am J Respir Crit Care Med* 2010; 181: 975–982.
115. Rady MY, Rivers EP, Nowak RM. Resuscitation of the critically ill in the ED: responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate. *Am J Emerg Med* 1996; 14: 218–225.
116. Walley KR. Use of central venous oxygen saturation to guide therapy. *Am J Respir Crit Care Med* 2011; 184: 514–520.
117. Vallet B, Robin E, Lebuffe G. Venous oxygen saturation as a physiologic transfusion trigger. *Crit Care* 2010; 14: 213.
118. Perner A, Haase N, Wiis J, *et al.* Central venous oxygen saturation for the diagnosis of low cardiac output in septic shock patients. *Acta Anaesthesiol Scand* 2010; 54: 98–102.
119. Pope JV, Jones AE, Gaieski DF, *et al.* Multicenter study of central venous oxygen saturation ($ScvO_2$) as a predictor of mortality in patients with sepsis. *Ann Emerg Med* 2010; 55: 40–46.
120. Castellanos-Ortega A, Suberviola B, Garcia-Astudillo LA, *et al.* Impact of the surviving sepsis campaign protocols on hospital length of stay and mortality in septic shock patients: results of a three-year follow-up quasi-experimental study. *Crit Care Med* 2010; 38: 1036–1043.
121. Chamberlain DJ, Willis EM, Bersten AB. The severe sepsis bundles as processes of care: a meta-analysis. *Aust Crit Care* 2011; 24: 229–243.
122. Ising P, Smith TW, Simpson SQ. Effect of intermittent *vs* continuous $ScvO_2$ monitoring on sepsis bundle compliance and mortality. *Chest* 2009; 136: 21S.
123. Nolt BR, Gonzales R, Maselli J, *et al.* Vital-sign abnormalities as predictors of pneumonia in adults with acute cough illness. *Am J Emerg Med* 2007; 25: 631–636.
124. Wu CL, Lin FJ, Lee SY, *et al.* Early evolution of arterial oxygenation in severe community-acquired pneumonia: a prospective observational study. *J Crit Care* 2007; 22: 129–136.
125. Walden AP, Young JD, Sharples E. Bench to bedside: a role for erythropoietin in sepsis. *Crit Care* 2010; 14: 227.
126. Yalavatti GS, DeBacker D, Vincent JL. Assessment of cardiac index in anemic patients. *Chest* 2000; 118: 782–787.
127. Sakr Y, Chierego M, Piagnerelli M, *et al.* Microvascular response to red blood cell transfusion in patients with severe sepsis. *Crit Care Med* 2007; 35: 1639–1644.
128. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. *Crit Care Med* 2008; 36: 2667–2674.

129. Vincent JL, Sakr Y, Sprung C, *et al.* Are blood transfusions associated with greater mortality rates? Results of the sepsis occurrence in acutely ill patients study. *Anesthesiology* 2008; 108: 31–39.
130. Park DW, Chun BC, Kwon SS, *et al.* Red blood cell transfusions are associated with lower mortality in patients with severe sepsis and septic shock: a propensity-matched analysis. *Crit Care Med* 2012; 40: 3140–3145.
131. Takanishi DM, Yu M, Lurie F, *et al.* Peripheral blood hematocrit in critically ill surgical patients: an imprecise surrogate of true red blood cell volume. *Anesth Analg* 2008; 106: 1808–1812.
132. Parrillo JE. Cardiovascular dysfunction in septic shock: new insights into a deadly disease. *Int J Cardiol* 1985; 7: 314–321.
133. Afessa B, Abdulai RM, Kremers WK, *et al.* Risk factors and outcome of pulmonary complications after autologous hematopoietic stem cell transplant. *Chest* 2012; 141: 442–450.
134. Rivers EP, McCord J, Otero R, *et al.* Clinical utility of B-type natriuretic peptide in early severe sepsis and septic shock. *J Intensive Care Med* 2007; 22: 363–373.
135. Nasraway SA, Rackow EC, Astiz ME, *et al.* Inotropic response to digoxin and dopamine in patients with severe sepsis, cardiac failure, and systemic hypoperfusion. *Chest* 1989; 95: 612–615.
136. Walkey AJ, Wiener RS, Ghobrial JM, *et al.* Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA* 2011; 306: 2248–2254.
137. Nguyen HB, Rivers EP, Knoblich BP, *et al.* Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med* 2004; 32: 1637–1642.
138. Nguyen HB, Corbett SW, Steele R, *et al.* Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Crit Care Med* 2007; 35: 1105–1112.
139. Falk JL, Rackow EC, Leavy J, *et al.* Delayed lactate clearance in patients surviving circulatory shock. *Acute Care* 1985; 11: 212–215.
140. Jones AE, Shapiro NI, Trzeciak S, *et al.* Lactate clearance *vs* central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA* 2010; 303: 739–746.
141. Dugas AF, Mackenhauer J, Salciccioli JD, *et al.* Prevalence and characteristics of nonlactate and lactate expressors in septic shock. *J Crit Care* 2012; 27: 344–350.
142. Rivers EP, Elkin R, Cannon CM. Counterpoint: should lactate clearance be substituted for central venous oxygen saturation as goals of early severe sepsis and septic shock therapy? No. *Chest* 2011; 140: 1408–1413.
143. Alhazzani W, Jacobi J, Sindi A, *et al.* The effect of selenium therapy on mortality in patients with sepsis syndrome: A systematic review and meta-analysis of randomized controlled trials. *Crit Care Med* 2013; 41: 1555–1564.
144. Ware LB, Fang X, Matthay MA. Protein C and thrombomodulin in human acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 2003; 285: L514–L521.
145. Cruz DN, Antonelli M, Fumagalli R, *et al.* Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. *JAMA* 2009; 301: 2445–2452.
146. Rivers EP, Jaehne AK, Nguyen HB, *et al.* Early biomarker activity in severe sepsis and septic shock and a contemporary review of immunotherapy trials: not a time to give up, but to give it earlier. *Shock* 2013; 39: 127–137.
147. Castellanos-Ortega A, Suberviola B, Garcia-Astudillo LA, *et al.* Impact of the surviving sepsis campaign protocols on hospital length of stay and mortality in septic shock patients: results of a 3-year follow-up quasi-experimental study. *Crit Care Med* 2010; 38: 1036–1043.
148. Kortgen A, Niederprum P, Bauer M. Implementation of an evidence-based "standard operating procedure" and outcome in septic shock. *Crit Care Med* 2006; 34: 943–949.
149. Zubrow MT, Sweeney TA, Fulda GJ, *et al.* Improving care of the sepsis patient. *Jt Comm J Qual Patient Saf* 2008; 34: 187–191.
150. Focht A, Jones AE, Lowe TJ. Early goal-directed therapy: improving mortality and morbidity of sepsis in the emergency department. *Jt Comm J Qual Patient Saf* 2009; 35: 186–191.
151. Coba V, Whitmill M, Mooney R, *et al.* Resuscitation bundle compliance in severe sepsis and septic shock: improves survival, is better late than never. *J Intensive Care Med* 2011; 26: 304–313.
152. Castellanos-Ortega A, Suberviola B, Garcia-Astudillo LA, *et al.* Late compliance with the sepsis resuscitation bundle: impact on mortality. *Shock* 2011; 36: 542–547.

Chapter 15

Early outcomes in CAP: clinical stability, clinical failure and nonresolving pneumonia

Stefano Aliberti and Paola Faverio

SUMMARY: Clinical stability is the first step of clinical improvement in patients with pneumonia. Clinical stability has been proven to be useful in guiding the switch of antibiotic therapy from intravenous to oral formulations. Given its importance in patient management, several sets of criteria have been created to standardise its definition. However, a single set of criteria cannot fit everybody; therefore, a personalised approach based on the resolution of the patient's most prominent clinical features should be considered. Moreover, it is important to choose the set of criteria that best fits the standard of care at each site of practice. Clinical failure is considered a predictive factor of adverse clinical outcomes. The identification of the aetiology of clinical failure is important to determine the subsequent patient management. The term "nonresolving pneumonia" is used to indicate a failure to improve without clinical deterioration. Few epidemiological data have been published on this condition. Therefore, future studies should specifically address this topic.

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Once empirical antibiotic therapy has been started, patients with community-acquired pneumonia (CAP) can experience different clinical outcomes that mainly depend on the interaction among three different factors: 1) host characteristics (*e.g.* immune system, comorbidities and performance status); 2) pathogen characteristics (*e.g.* virulence, susceptibility and resistance to antimicrobials); and 3) antibiotic characteristics (*e.g.* timing, adequacy of therapy and pharmacokinetic factors). In light of the result of this interaction, severity of the disease can decrease and patients can experience a clinical improvement; conversely, severity can increase, leading to the patient's clinical deterioration, or it can remain at the same degree in comparison with baseline. The clinical response of hospitalised patients with CAP could thus be categorised into five possible outcomes (fig. 1). CAP patients may have an early clinical improvement (usually within the first 3 to 4 days after hospitalisation) or a late clinical improvement (within 7 days after hospitalisation). CAP patients may develop an early clinical deterioration (within the first 3 days of hospitalisation) or a late clinical deterioration (within 7 days after hospitalisation). If, after 7 days

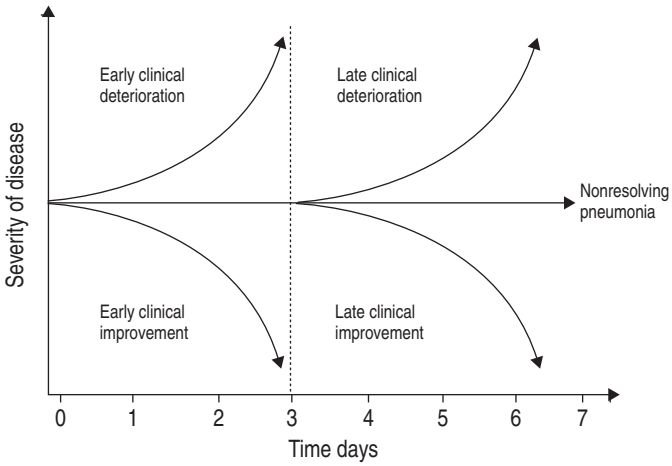

Figure 1. Clinical response in patients with community-acquired pneumonia.

of appropriate therapy, there is no evidence of clinical improvement or deterioration, patients are categorised as having nonresolving pneumonia [1].

Tools commonly used by physicians to follow-up CAP patients after initiation of antibiotic therapy include clinical variables (*e.g.* consciousness and delirium, cough, sputum production, chest pain, shortness of breath, fatigue or loss of appetite), markers of both systemic inflammation (temperature, white blood cell count, C-reactive protein or procalcitonin) and gas exchange (distress, respiratory rate, oxygen saturation or arterial oxygen tension). There are no fixed assessment tools to follow up a CAP patient, but those measures that are altered at baseline and that are readily available in the local clinical setting may be chosen.

Clinical improvement and clinical stability

Clinical improvement in CAP patients is a long process that involves different phases (fig. 2). It usually starts after initiation of appropriate antimicrobial therapy and supportive measures, and ends with the complete resolution of the infectious process and the patient's return to their usual daily activities. Despite being a continuous process, there are some crucial moments that need to be identified.

The first step in clinical improvement is the achievement of clinical stability. In the attempt to standardise this definition in clinical practice, several sets of criteria to identify patients that are clinically stable have been developed (table 1) [2–10].

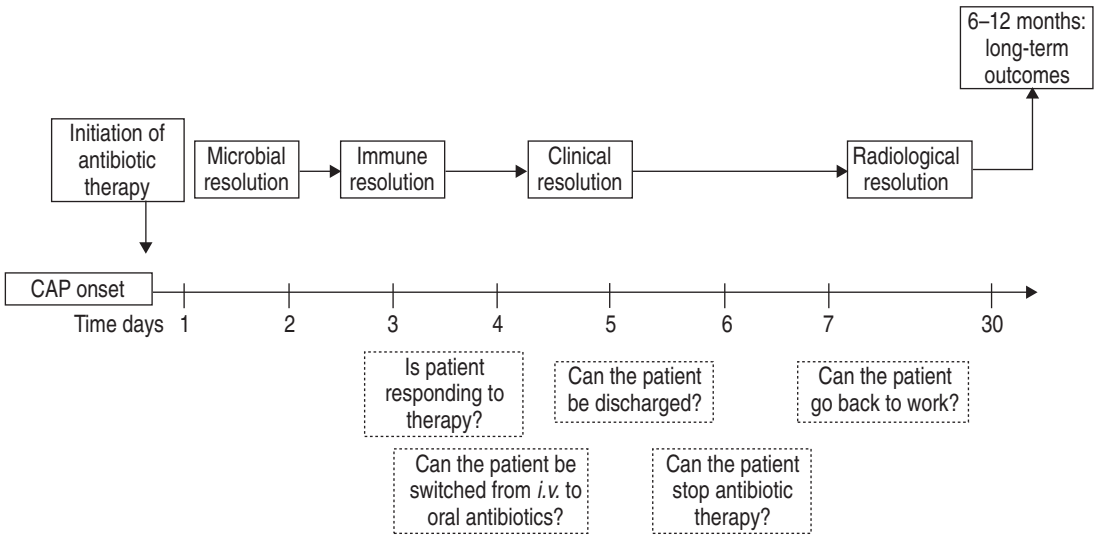

Figure 2. Improvement process in patients with community-acquired pneumonia (CAP).

Table 1. Criteria for clinical stability in patients with community-acquired pneumonia

First author [ref.]	Year	Definition	Criteria
NIEDERMAN [2]	2001	Criteria for switching from *i.v.* to oral antibiotic therapy	Improvement in cough and dyspnoea $T \leqslant 37.8$°C on two occasions 8 h apart WBC count decreasing at least 10% Adequate oral intake
WOODHEAD [3]	2011	Criteria for switching from *i.v.* to oral antibiotic therapy	Resolution of the most prominent clinical features at admission
MANDELL [4]	2007	Criteria for clinical stability	$T \leqslant 37.8$°C $f_C \leqslant 100$ beats·min^{-1} $f_R \leqslant 24$ breaths·min^{-1} SBP $\geqslant 90$ mmHg $S_{O_2} \geqslant 90\%$ or $P_{aO_2} \geqslant 60$ mmHg Ability to maintain oral intake Normal mental status
LIM [5]	2009	Features indicating response to initial empirical parenteral therapy permitting consideration of oral antibiotic substitution	Resolution of fever for >24 h $f_C < 100$ beats·min^{-1} Resolution of tachypnoea Clinically hydrated and taking oral fluids Resolution of hypotension Absence of hypoxia Improvement of WBC count Nonbacteraemic infection No microbiological evidence of *Legionella*, staphylococcal or Gram-negative enteric bacillus infection No concerns over gastrointestinal absorption
HALM [6]	1998	Clinical stability	Ability to eat Normal mental status $T \leqslant 38.3$°C $f_C \leqslant 100$ beats·min^{-1} SBP $\leqslant 90$ mmHg $f_R \leqslant 24$ breaths·min^{-1} $S_{O_2} \geqslant 90\%$
VAN DER EERDEN [7]	2004	Criteria for switching from *i.v.* to oral antibiotics	$T < 38$°C for 72 h Coughing with or without production of sputum, thoracic pain and dyspnoea have improved
MENÉNDEZ [8]	2004	Clinical stability	$T \leqslant 37.2$ °C $f_C \leqslant 100$ beats·min^{-1} $f_R \leqslant 24$ breaths·min^{-1} SBP $\geqslant 90$ mmHg $S_{pO_2} \geqslant 90\%$ or $P_{aO_2} \geqslant 60$ mmHg when the patient is not receiving supplemental oxygen; in patients with home oxygen therapy, stability is considered when their oxygen need is the same as prior to admission
SHINDO [9]	2008	Criteria for switching to oral antibiotics	$T \leqslant 37.8$°C for 16 h WBC count decreasing ($\leqslant 10\,000$ per mm^3) Adequate oral intake Improvement in cough and dyspnoea
MENÉNDEZ [10]	2009	Clinical stability	Same criteria as [8] plus PCT <0.25 ng·mL^{-1} CRP <3 mg·dL^{-1}

T: temperature; WBC: white blood cell; f_C: cardiac frequency; f_R: respiratory frequency; SBP: systolic blood pressure; S_{O_2}: oxygen saturation; P_{aO_2}: arterial oxygen tension; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; PCT: procalcitonin; CRP: C-reactive protein.

With such a wide choice of criteria and definitions, it may be difficult to select the most appropriate one. In some cases, even sets of criteria that consider the same parameters (*e.g.* temperature (*T*), cardiac frquency (f_C) and respiratory frequency (f_R)) but with a different cut-off

(*e.g.* T <38°C in one set and <37°C in another one) may focus on two different steps in the process of clinical improvement. In this sense, HALM and co-workers [6, 11] validated different sets of criteria to define clinical stability: from a more conservative (T ≤37.2°C, arterial oxygen saturation (S_{aO_2}) ≥94%, f_R ≤20 breaths·min^{-1}, systolic blood pressure (SBP) ≥90 mmHg, f_C ≤100 beats·min^{-1}, ability to eat and normal mental status) to a more lenient one (T ≤38.3°C, S_{aO_2} ≥90%, f_R ≤24 breaths·min^{-1}, SBP ≥90 mmHg, f_C ≤100 beats·min^{-1}, ability to eat and normal mental status). Patients evaluated with the less conservative definitions reached clinical stability significantly earlier than the others (3 *versus* 7 days). However, regardless of the clinical stability definition used, once a patient stabilises, the risk of serious clinical deterioration was ≤1%. Another recent study on adult hospitalised patients with CAP showed that the criteria recommended by the 2001 American Thoracic Society (ATS) guidelines identified clinical stability significantly earlier than those recommended by the 2007 ATS/Infectious Diseases Society of America (IDSA) guidelines [12]. These findings support the idea that different sets of criteria identify different phases of patient improvement [1].

Two ideas should be taken into consideration to choose criteria to define clinical stability in clinical practice: patients' characteristics, local tools and standard operating procedures.

On one hand, a single set of criteria cannot fit every patient with CAP and some of them may have atypical pneumonia presentations (*e.g.* pleuritic chest pain without fever and without increased white blood cell (WBC) count). In deciding to switch from intravenous to oral antibiotic treatment, the 2011 European Respiratory Society (ERS) guidelines suggest following the resolution of patients' most prominent clinical features on admission. Special groups of subjects may particularly benefit from this personalised method to assess clinical stability. Elderly, frail patients, for example, may have acute changes in cognitive and/or functional status as a unique sign of pneumonia at presentation and the resolution of this symptom will indicate the achievement of clinical stability [13]. In immunocompromised patients, the identification of clinical stability is an important challenge for physicians. Some parameters, such as WBC count, may be normal in these patients throughout the course of the acute infectious disease due to the alteration of the immune response. Only few observations evaluating clinical stability criteria have been made in immunocompromised patients, since immunosuppression is commonly an exclusion criteria for studies evaluating treatment of CAP patients. VIALE *et al.* [14] evaluated the percentage of patients who deteriorated after reaching clinical stability in a cohort of 437 HIV-positive patients with pneumonia. The authors used different sets of criteria to define clinical stability: a more lenient definition (SBP >90 mmHg, f_C <100 beats·min^{-1}, f_R <24 breaths·min^{-1}, S_{aO_2} >90%, T <38°C, spontaneous feeding and normal mental status) and a more conservative one (SBP >90 mmHg, f_C <90 beats·min^{-1}, f_R <20 breaths·min^{-1}, S_{aO_2} >94%, T <37°C, spontaneous feeding and normal mental status). When the most conservative definition was applied, 2% of the patients had clinical deterioration after stabilisation and none of them died. When the least conservative definition was used, 7% of the patients had a clinical deterioration after stabilisation and four of them died. Given the paucity of data, a conservative set of criteria appears to be safer in immunocompromised subjects. Future studies on clinical stability should target this special group of patients.

On the other hand, it is important to choose the set of criteria that best fits the standard of care in each site of practice [15]. This is particularly the case for laboratory measurements of systemic inflammation, such as C-reactive protein (CRP) or procalcitonin (PCT). Adding biomarkers may improve the performance of criteria to determine clinical stability. MENÉNDEZ *et al.* [10] found that low levels of CRP and PCT, in addition to clinical criteria, might improve the prediction of the absence of severe complications in hospitalised patients with CAP. The effect of immune deficit on PCT levels is still a subject of controversy [16, 17]. However, adding markers of systemic infection/inflammation to other clinical and laboratory parameters may serve as an additional tool to help recognise clinical stability in immunocompromised patents.

The definition of a fixed set of criteria of clinical stability in CAP patients is of crucial importance from an investigational point of view. To evaluate the superiority of one antibiotic over another in

clinical trials, several studies have considered clinical stability as an early outcome, using the most common parameters found in clinical practice [18].

Time to clinical stability

Time to clinical stability is defined as the time from antibiotic therapy initiation to the first day in which all the criteria used to identify clinical stability are reached. In an immunocompetent patient with CAP, clinical improvement is usually reached around day 3 [1]. Up to two-thirds of all CAP patients had clinical improvement and met criteria for clinical stability in the first 3 days of hospitalisation, and most non-intensive care unit (ICU) patients met the criteria by day 7 [4]. Among immunocompetent patients, the 3-day cut-off seems to fit with the different phases of pneumonia resolution. After 3 days of adequate antimicrobial therapy, immune resolution has already started (reduction of inflammatory and infection markers) and the patient is moving towards clinical resolution (improvement of symptoms due to pneumonia) (fig. 2).

Different studies highlighted a number of conditions associated with prolonged time to clinical stability (table 2) [4, 6, 8, 19]. Such conditions can be referred to three main groups: high severity of disease (*e.g.* concomitant parapneumonic effusion, multilobar involvement and respiratory failure), treatment failure (*e.g.* resistant pathogens or nosocomial superinfections) and host factors (*e.g.* multiple comorbidities and advanced age). HIV infection does not seem to influence time to clinical stability in hospitalised patients with CAP [14, 20]. On the contrary, some pathogens, such as *Pneumocystis jiroveci* infection in HIV-positive patients, and invasive infections (*e.g.* bacteraemia) are correlated with a delayed time to clinical stability [14, 21]. Cavitation has also been associated with prolonged time to clinical stability [1]. To our knowledge, the only factor associated with a positive effect on clinical stability is the adherence to treatment guidelines [8].

Why is the identification of clinical stability important?

Clinical stability criteria have been proved to be useful in guiding the switch of antibiotic therapy from *i.v.* to oral formulations [4, 5, 22]. An early switch to oral antibiotic therapy may present clinical advantages, including lower risk of phlebitis, line sepsis, fluid overload and earlier mobilisation, as well as economic benefits, such as earlier discharge [23]. The most recent guidelines, such as the 2007 ATS/IDSA and 2009 British Thoracic Society (BTS) recommendations, provided their own sets of criteria to determine clinical stability and to consider switching to oral therapy (table 1) [4, 5]. The 2007 ATS/IDSA guidelines suggested switching patients from *i.v.* to oral therapy when they are haemodynamically stable, improving clinically,

Table 2. Factors associated with a delay in reaching clinical stability in patients with community-acquired pneumonia

First author [ref.]	Year	Factors
MENÉNDEZ [8]	2004	Dyspnoea Confusion Chronic bronchitis Pleural effusion and/or empyema Multilobar pneumonia Treatment failure ICU admission Cardiac and/or respiratory complications
HALM [6]	1998	PSI risk classes IV and V
ARNOLD [19]	2010	Higher PSI risk classes Higher CURB65 scores
MANDELL [4]	2007	Advanced age Multiple comorbidities Resistant or uncovered pathogens Parapneumonic effusion/empyema Nosocomial superinfections Noninfectious complications

ICU: intensive care unit; PSI: Pneumonia Severity Index; CURB65: confusion, urea >7 mmol·L^{-1}, respiratory frequency ≥ 30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) or ≤ 60 mmHg (diastolic), age ≥ 65 years.

able to ingest medications and have a normally functioning gastrointestinal tract [4]. Clinical stability and switching to oral antibiotic criteria could be met simultaneously or sequentially. Once hospitalised patients with CAP reach clinical stability, it is safe to switch from *i.v.* to oral therapy even in severe or complicated cases. RAMIREZ *et al.* [22] showed that this principle can be safely applied in patients with CAP complicated by *Streptococcus pneumoniae* bacteraemia.

Clinical stability may help physicians to decide whether to discharge CAP patients. According to the most recent guidelines, patient discharge should depend mainly on the achievement of clinical stability and on having all the medications switched from the *i.v.* to the oral route [4, 5]. In everyday practice, physicians usually prefer to observe patients for at least 1 day after switching to oral therapy [4]. However, the benefits of this common practice have not been proved and it may increase healthcare costs [24]. A recent study also indicates that the time to clinical stability in patients with CAP during the hospital course is significantly associated with adverse outcomes after discharge [25]. Patients with CAP who experienced a delay in reaching clinical stability during hospitalisation had a higher risk of adverse outcomes within 30 days after discharge.

Based on some expert opinions, clinical stability criteria might also guide physicians in decide the duration of antibiotic therapy, but evidence in this regard is still scarce. The optimal duration of antimicrobial therapy in CAP is not yet known. The 2009 BTS and 2011 ERS guidelines proposed 7–10 days of treatment for most patients with CAP [3, 5]. However, the 2007 ATS/IDSA guidelines recommended discontinuing antibiotic treatment after at least 5 days of therapy, if patients are afebrile and with one or fewer CAP-associated signs of instability [4]. The duration of antibiotic treatment may need to be prolonged in patients receiving initial inadequate antibiotic therapy, patients with extrapulmonary or complicated infections (*e.g. Staphylococcus aureus* bacteraemia complicated by endocarditis), and patients with necrotising pneumonia or other signs of necrosis due to poor antibiotic penetration [4]. Traditionally, duration of antimicrobial therapy also depended upon the pathogen isolated; an example of such practice is Legionnaires' disease, in which prolonged antibiotic therapy of 2 to 3 weeks was recommended [5]. However, the most recent BTS guidelines suggested that, even in this case, there is not enough evidence to support a prolonged antibiotic therapy *a priori* and the duration of antibiotics should be guided by clinical judgment, as all the other cases [5]. Other instruments that may help to decide duration of antibiotic treatment are biomarkers; several studies have recently been published on the use of PCT for this purpose [26].

Definition of treatment failure and clinical failure

Several definitions of "failure" in patients with CAP have been developed, based on clinical and laboratory parameters, as well as vital signs and radiological findings (table 3) [27–36]. The term "treatment failure" has been used mainly to evaluate the response of patients to antimicrobial treatment [1]. The term "clinical failure" refers to clinical deterioration of patients with CAP (*e.g.* acute respiratory failure or septic shock), regardless of specific causes (*e.g.* treatment failure or superimposed infections) [1].

Aetiologies and management of clinical failure

The identification of the aetiology of clinical failure is crucial for the subsequent management of CAP patients. Clinical failure aetiology may be classified into host-related, drug-related and pathogen-related causes [30]. A prospective, observational study by GENNÉ *et al.* [37] on 228 patients hospitalised for CAP showed that host-related complications were the most common (61%). Other authors created different classifications of clinical failure that included pneumonia-related *versus* non-pneumonia-related [33] and infectious *versus* noninfectious aetiologies [8, 37], with infectious causes and those related to pneumonia being the main contribution to the aetiology of clinical failure (table 4). In particular, development of severe sepsis and progression

Table 3. Definitions of clinical and treatment failure in patients with community-acquired pneumonia (CAP)

First author [ref.]	Year	Definition	Criteria
Arancibia [27]	2000	Nonresponding pneumonia	Persisting fever >38°C and/or clinical symptoms after at least 72 h of antimicrobial treatment
		Progressive pneumonia	Acute respiratory failure requiring ventilatory support and/or septic shock after at least 72 h of antibiotic therapy
Menéndez [28]	2004	Early treatment failure	Clinical deterioration within 72 h of treatment resulting from one or more of the following causes: haemodynamic instability, appearance of respiratory failure, need for mechanical ventilation, radiographic progression or the appearance of new metastatic infectious foci
		Late treatment failure	Persistence or reappearance of fever and symptoms or haemodynamic instability, development of respiratory failure, radiographic progression or appearance of new infectious foci after 72 h of antimicrobial treatment
Rosón [29]	2004	Early failure	Lack of response or worsening of clinical and/or radiological status at 48–72 h, requiring either changes in antibiotic therapy or performance of invasive procedures for diagnostic and therapeutic purposes
		Progressive respiratory failure	Increasing oxygen requirements or the necessity of mechanical ventilation during follow-up
Hoogewerf [30]	2006	Early clinical failure	Death, need for ventilation, f_R >25 breaths·min^{-1}, S_{pO_2} <90%, P_{aO_2} <55 mmHg, haemodynamic instability, altered mental state, fever
Kaye [31]	2008	Treatment failure	The persistence of symptoms after the first week following the office visit, necessitating hospitalisation related to persistent or worsening pneumonia
Ye [32]	2008	Outpatient treatment failure	Occurrence of one of the following: a second antibiotic claim after the index prescription date or hospital admission with a primary or secondary diagnosis of CAP
Aliberti [33]	2008	Clinical failure	Acute pulmonary deterioration with the need for ventilator support; acute haemodynamic deterioration with the need for aggressive fluid resuscitation, vasopressors or invasive procedures; in-hospital death
			Early clinical failure: occurring ⩽3 days after hospital admission
			Late clinical failure: occurring >3 days after hospital admission
		Clinical failure related to CAP	Failure with aetiology directly related to the pulmonary infection and its systemic inflammatory response
		Clinical failure unrelated to CAP	Failure with aetiology unrelated to the pulmonary infection and its systemic inflammatory response
Menéndez [34]	2008	Early treatment failure	Clinical deterioration within 72 h of treatment, as indicated by the need for mechanical ventilation, or shock or death
		Late treatment failure	Persistence or reappearance of fever, radiographic progression, including pleural effusion or empyema, nosocomial infection, respiratory failure, need for mechanical ventilation or septic shock after 72 h
Hess [35]	2010	Treatment failure	Refill for the index antibiotic after completed days of therapy, a different antibiotic dispensed >1 day after the index prescription, or hospitalisation with a pneumonia diagnosis or emergency department visit >3 days postindex
Ott [36]	2012	Treatment failure	Need to switch to another antibiotic regimen ⩾72 h after initial treatment resulting in an expansion of the antibiotic spectrum by adding another agent or replacing the initial antibiotic by another of the same class with a broader antibacterial spectrum

f_R: respiratory frequency; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; P_{aO_2}: arterial oxygen tension.

Table 4. Causes of clinical failure in patients with community-acquired pneumonia (CAP)

First author [ref.]	Year	Definition	Causes
Rosón [29]	2004	Early clinical failure	Progressive pneumonia 67% (including radiological progression and respiratory failure) Pleural empyema 22% Lack of response 16% Uncontrolled sepsis 11% Nosocomial infection (HAP) 4% Patients with more than one cause of failure 25%
Aliberti [33]	2008	Clinical failure	Clinical failure related to CAP 81%: Severe sepsis 33% Acute myocardial infarction 28% Progressive pneumonia 19% Exacerbation of CHF 9% Cardiac arrhythmia 4% Endocarditis 2% Empyema 2% Acute exacerbation of COPD 2% Pulmonary embolism 2% Mucus plug 2% Clinical failure unrelated to CAP 13%: HAP 45% Iatrogenic pneumothorax due to CVC 11% Benzodiazepine overdose-induced respiratory failure 11% Gastro-intestinal bleeding 11% Aspiration of gastric content 11% Iatrogenic bleeding in pleural space 11% Idiopathic 6%
Arancibia [27]	2000	Treatment failure	Persistent infections 24% Primary infections 19% Nosocomial infections 20% Malignancy 6% Interstitial lung disease (*e.g.* BOOP) 6% Cardiopathy 4% Foreign body 2% Idiopathic or nondiagnostic 20%
Menéndez [28]	2004	Overall treatment failure	Infectious causes 40% Noninfectious causes 16% Undetermined 44%
Genné [38]	2003	Treatment failure	Undefined causes 57% Antibiotic side-effect 30% Resistant microorganism 6% Death 3% Nosocomial superinfection 2% Pleural empyema 1% Underlying pulmonary disease (*e.g.* obstructive tumour) 1%
Genné [37]	2006	Treatment failure	Incorrect diagnosis 5% Host-related problems 61%: Inadequate host response 20% Empyema 13% Respiratory failure 8% Superinfection 7% Pulmonary embolism 4% Unresponsive shock 4% Heart insufficiency 3% Cerebral palsy 2% Drug-related problems 18%: Adverse drug reaction (cutaneous reaction) 13% Error in drug selection 3% Poor compliance (<75% of antibiotics taken) 2% Pathogen-related problems 16%: Other pathogenic organisms (*Mycobacterium tuberculosis*) 16% Undetermined 16%

HAP: hospital-acquired pneumonia; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; CVC: central venous catheter; BOOP: bronchiolitis obliterans organising pneumonia.

of pneumonia seem to be the two most common causes of clinical failure [27–29, 33]. Aetiologies of clinical failure also vary according to the time of onset. Early clinical failure (<72 h of treatment) is associated with a higher severity of the disease at baseline, inaccurate diagnosis and factors directly related to the infection (*e.g.* resistant microorganism or empyema). Delayed clinical failure (>72 h) is less likely to be directly associated with the primary infection but more likely to be associated with its management (*e.g.* exacerbation of comorbid illnesses, concomitant noninfectious disease and nosocomial superinfection). All the studies and classifications were meant to help clinicians to understand the mechanisms of clinical failure and, ultimately, to improve clinical management. Table 5 summarises all the different scenarios that need to be considered when evaluating a patient with CAP and clinical failure. Priority should be given to the formulation of hypotheses regarding the aetiology of clinical failure and to the institution of measures of management accordingly.

Despite progress in the knowledge of the mechanisms of clinical failure, in some cases, the aetiology remains unknown. GENNÉ *et al.* [38] reviewed all the causes of treatment failure in CAP clinical trials published between 1990 and 1997, and reported that in 57% of the cases, the aetiology of failure could not be determined. In more recent studies, the percentage of clinical failure cases whose aetiology was not identified varies widely, ranging from 0% to 44% [27–29, 33, 37, 39]. Therefore, future studies should aim to identify possible aetiologies of clinical failure that are still unknown.

Cardiovascular events are common complications and common causes of clinical failure in patients with CAP [40, 41]. Possible mechanisms that explain the causal association between pneumonia and cardiovascular events are hypoxaemia, systemic inflammatory response, bacterial/viral infection of the myocardium/pericardium, a procoagulant state, sympathetic activation and arrhythmogenic drugs [42]. CORRALES-MEDINA *et al.* [43] followed up 2287 adult patients with CAP for 30 days after presentation. Incident cardiac complications occurred in 358 (27%) inpatients and 20 (2%) outpatients. Although most events were diagnosed within the first week, more than half of them were recognised in the first 24 h. Worsening chronic heart failure (CHF) (67%), new or worsening arrhythmias (22%) and myocardial infarction (4%) were the most

Table 5. Management of clinical failure in patients with community-acquired pneumonia

To be considered
Incorrect diagnosis or complicating conditions
Rule out noninfectious process such as pulmonary infarction, pulmonary oedema, lung carcinoma, cryptogenic organising pneumonia, pulmonary alveolar haemorrhage, eosinophilic pneumonia
Progression of the infectious/inflammatory process, *e.g.* parapneumonic effusion, empyema, lung abscess, septicaemia
Other infectious sources and/or nosocomial superinfections, *e.g.* UTI due to urinary catheter, acute exacerbation of bronchiectasis
Impaired local or systemic defences, *e.g.* HIV infection, hypogammaglobulinaemia, myeloma, endobronchial obstruction
To be performed
A more extensive microbiological work-up, *e.g.* consider less common pathogens such as viruses and *Mycobacteria* spp.
An expansion of antimicrobial coverage, *e.g.* clinical suspicion of MDR or less common pathogens
A more extensive diagnostic work-up, *e.g.* bronchoscopy, ultrasonography and/or computed tomography scan
Optimisation of adjuvant therapies, *e.g.* nutritional assessment, hydration and oxygen support
Stabilisation and treatment of medical comorbidities, *e.g.* concomitant CHF and COPD exacerbations
To be reassessed
Duration, doses, route, drug interactions of the selected antimicrobial agents, *e.g.* adjust antibiotic dosage according to creatinine clearance; proarrhythmic effect of macrolides and fluoroquinolones due to possible QT prolongation; inadequate absorption of antibiotics by oral route

UTI: urinary tract infection; MDR: multidrug-resistant; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease.

common complications recognised. Special attention must be paid to prevention and early recognition of cardiovascular events in patients with pneumonia, in particular in those who have other concomitant risk factors.

Predictors of failure

Predictive factors of clinical failure have been widely investigated, as shown in table 6 [28–30, 34, 37, 44]. These conditions are mainly related to the severity of the disease, comorbidities, complications related to pneumonia (*e.g.* pleural effusion) and the appropriateness of antimicrobial therapy. Furthermore, ROSÓN *et al.* [29] described some pathogen-related characteristics associated with clinical failure: *Legionella* and Gram-negative pneumonia seemed to be associated with increased risk of clinical failure. Conditions inversely related to clinical failure have also been described. Chronic obstructive pulmonary disease (COPD), CHF and older age are among these [28–30].

Table 6. Factors associated with clinical or treatment failure in patients with community-acquired pneumonia

First author [ref.]	Year	Definition	Increased risk of failure	Decreased risk of failure
MENÉNDEZ [28]	2004	Overall failure	Liver disease Pleural effusion Multilobar infiltrates Cavitation Leukopenia Higher PSI risk class	Influenza vaccination Initial treatment with fluoroquinolones COPD
ROSÓN [29]	2004	Early failure[#]	Multilobar infiltrates High PSI risk class (score >90) *Legionella* pneumonia Gram-negative pneumonia Inappropriate antimicrobial therapy	Age >65 years Appropriate antimicrobial therapy
GENNÉ [37]	2006	Overall failure	Concomitant malignancy Anamnestic aspiration pneumonia Neurological disease	Elevated monocytes
MENÉNDEZ [34]	2008	Overall failure Early failure[#]	IL-6 above cut-off point (169 pg·mL^{-1}) on day 1 IL-8 above cut-off point (14 pg·mL^{-1}) on day 1 CRP above cut-off point (21.9 mg·dL^{-1}) on day 1 Increased PCT values on day 1	
OSTER [44]	2013	Early failure[#]	Malnourishment, renal failure, CHF, CVD, immunosuppression and liver disease Leukopenia, thrombocytopenia, hyperglycaemia, hyponatraemia, acidosis, uraemia, anaemia, hypoxaemia on admission Pneumonia admission in previous 12 months Receipt of vasoactive medications, endotracheal intubation, mechanical ventilation and/or central venous catheter within 24 h of admission Time to first dose of *i.v.* antibiotic therapy >8 h	
HOOGEWERF [30]	2006	Late failure[¶]	Altered mental status Arterial pH <7.35 mmHg P_{aO_2} <60 mmHg	Chronic heart failure

PSI: Pneumonia Severity Index; IL: interleukin; CRP: C-reactive protein; PCT: procalcitonin; CVD: cardiovascular disease; P_{aO_2}: arterial oxygen tension; COPD: chronic obstructive pulmonary disease. [#]: within 72 h from admission; [¶]: after 72 h from admission, only in patients with severe community-acquired pneumonia (PSI score >90 or according to the 2007 American Thoracic Society/Infectious Diseases Society of America definition [4]).

Clinical failure itself is a predictive factor of adverse clinical outcomes. In-hospital mortality of patients with treatment failure can be as high as 43% [27]. A recent study by OSTER *et al.* [44] showed that treatment failure was associated with higher in-hospital mortality rate compared with CAP patients without treatment failure (8.5% *versus* 3.3%, respectively), longer hospital stay (mean ± SD 10.1 ± 8.1 *versus* 4.9 ± 3.3 days, respectively) and higher healthcare costs. HOOGEWERF *et al.* [30] reported a higher 28-day mortality rate in patients with severe CAP who failed to respond to treatment compared with responders (12% *versus* 4.4%, respectively). Length of *i.v.* antibiotic therapy, need for admission to the ICU and rate of complications were also significantly higher in patients who developed clinical failure [28–30].

Definitions of nonresolving pneumonia, nonresponding pneumonia and slow-resolving pneumonia

Nonresolving pneumonia is characterised by the presence of signs and symptoms compatible with respiratory infection and infiltrates on chest radiography that persist after the initiation of antibiotic therapy [1]. The term "nonresolving pneumonia" is different from clinical failure, as the patient's clinical status is neither improving nor deteriorating. No standardised cut-off to define nonresolving pneumonia in terms of timing exists in the literature. Some authors have suggested a cut-off of a minimum of 10 days of antibiotic treatment [45], while the 2007 ATS/IDSA guidelines defined nonresolving pneumonia as the persistence of pulmonary infiltrates >30 days after symptom onset [4]. Alternative diagnoses should be suspected in patients with nonresolving pneumonia, including lung cancer, and further invasive diagnostic tests (*e.g.* bronchoscopy with biopsies) should be considered [46].

"Slow-resolving pneumonia" and "persistent pneumonia" are two terms usually used synonymously with nonresolving pneumonia to indicate failure to improve without clinical deterioration. The term "nonresponding pneumonia" has recently been used in some of the main guidelines and is defined as a situation in which an inadequate clinical response is present despite antibiotic treatment [3, 4]. A failure to improve in the first 72 h after initiation of antibiotic treatment is considered a normal response, because most patients require at least 72 h to achieve clinical stability. Failure to improve after 72 h from antibiotic initiation may be considered nonresponding pneumonia and is associated with a prolonged time to clinical stability.

All these classifications are meant to help determine an aetiology and guide management. The 2011 ERS guidelines consider factors related to the pathogen and the host immune defences (*e.g.* antimicrobial resistance or uncovered pathogens), the main causes of early nonresponding pneumonia [3]. As for clinical failure, factors not directly related to pneumonia but related to its management (*e.g.* nosocomial superinfections and concomitant noninfectious disease, including misdiagnosis) seem to be the most common causes of delayed nonresponding pneumonia [3, 4].

Aetiology and management of nonresolving pneumonia

The differentiation of clinical failure from nonresolving pneumonia may sometimes be difficult. The most reliable tool to differentiate these two conditions is clinical examination (rapid deterioration *versus* slow deterioration or unchanged conditions). Laboratory markers of infection/inflammation, such as WBCs, CRP and PCT, could also play a role. A study by RUIZ-GONZÁLEZ *et al.* [47] evaluated the CRP levels in 285 patients with pneumonia that did not reach clinical stability by day 4; the authors found that CRP levels were useful to discriminate between true treatment failure (CRP levels unchanged or increased) and slow response to treatment (CRP levels reduced).

Resolution of radiographic infiltrates in patients with pneumonia usually requires 4–8 weeks [48]. The majority of clinical stability criteria do not include the evaluation of radiographic imaging. Therefore, chest radiographic exams are not usually repeated in the early phase of CAP treatment,

unless the patient deteriorates or does not reach clinical stability. In a study by EL SOLH *et al.* [49], the rate of radiographic clearance in immunocompetent elderly patients (aged 70 years or more) with CAP was estimated at 35% within 3 weeks, 60% within 6 weeks and 84% within 12 weeks. Multivariate regression analysis demonstrated that high comorbidity index and multilobar disease had independent predictive value for slow radiographic resolution. The authors recommended a waiting period of 12 to 14 weeks for slow-resolving pneumonia to be considered nonresolving. Several factors have been associated with delayed radiographic resolution of pneumonia: severity of the disease, history of smoking, advanced age, extent of involvement (multilobar), persistent fever or leukocytosis [50]. Coexisting medical conditions impairing immune function, such as diabetes, COPD, renal failure and alcohol abuse, may slow normal clearing of infiltrates [50]. Moreover, less common infectious agents (*e.g.* tuberculosis or fungi), conditions that mimic pneumonia (*e.g.* neoplasm or CHF) and pulmonary complications (*e.g.* abscess) may also result in delayed resolution [50]. A recent study by JAYAPRAKASH *et al.* [39] evaluated the morbid conditions associated with nonresolving pneumonia in 70 patients who did not show improvement after 2 weeks of adequate antibiotics. The authors found that tuberculosis (36%) and malignancy (27%) were the causative factor in more than 50% of the cases. ''Middle lobe syndrome'' is another cause of recurrent or slow-resolving pneumonias. Main causes of the syndrome are ventilation disorders of the middle lobe that can be both intrinsic (*e.g.* endobronchial tumours) and extrinsic (*e.g.* lymphadenopathy). Bronchial obstruction causes atelectasis and poor airway clearance that leads to slow-resolving/recurrent infections.

Invasive techniques can be deferred when unequivocal, although incomplete, radiographic resolution can be demonstrated within 8 weeks, particularly in patients with risk factors for slow resolution. In this case, close radiological and clinical follow-up is warranted. However, lack of at least partial radiographic resolution by 6 weeks, even in asymptomatic patients, deserves further investigation [46], but a lack of evidence regarding this topic makes any kind of recommendation weak and based mainly on expert opinion.

Most authors consider fibreoptic bronchoscopy and computed tomography useful first steps in the evaluation of nonresolving pneumonia [51]. However, despite the large interest that has recently emerged around clinical failure, few epidemiological studies have been published on nonresolving pneumonia. Therefore, future research should specifically address this topic. In the meantime, most of the management and therapeutic options applicable to clinical failure can also be suitable for nonresolving pneumonia (table 5).

Conclusions

Clinical stability is the first step of clinical improvement in patients with pneumonia. Clinical stability helps clinicians to identify the best candidates for switching from *i.v.* to oral antibiotic therapy and for hospital discharge. Given its importance in patient management, several sets of criteria have been created to standardise the definition of clinical stability. However, a single set of criteria cannot fit everybody; therefore, a personalised approach based on the resolution of the patient's most prominent clinical features on admission should be considered. Moreover, it is important to choose the set of criteria that best fits the standard of care in each site of practice. Clinical failure is considered a predictive factor of adverse clinical outcomes. Identification of the aetiology of clinical failure is important to determine the subsequent patient management. Knowledge of the risk factors associated with the development of clinical failure, its prompt recognition and adequate management are likely to improve CAP patients' outcomes, including mortality and hospital length of stay. Finally, the term nonresolving pneumonia is used to indicate a failure to improve without clinical deterioration. Few epidemiological data have been published on this condition. Therefore, future studies should specifically address this topic.

Statement of Interest
None declared.

References

1. Aliberti S, Blasi F. Clinical stability *versus* clinical failure in patients with community-acquired pneumonia. *Semin Respir Crit Care Med* 2012; 33: 284–291.
2. Niederman MS, Mandell LA, Anzueto A, *et al.* Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001; 163: 1730–1754.
3. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections – full version. *Clin Microbiol Infect* 2011; 17: Suppl. 6, E1–E59.
4. Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44: Suppl. 2, S27–S72.
5. Lim WS, Baudouin SV, George RC, *et al.* BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; 64: Suppl. 3, iii1–iii55.
6. Halm EA, Fine MJ, Marrie TJ, *et al.* Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. *JAMA* 1998; 279: 1452–1457.
7. Van der Eerden MM, de Graaff CS, Vlaspolder F, *et al.* Evaluation of an algorithm for switching from IV to PO therapy in clinical practice in patients with community-acquired pneumonia. *Clin Ther* 2004; 26: 294–303.
8. Menéndez R, Torres A, Rodríguez de Castro F, *et al.* Reaching stability in community-acquired pneumonia: the effects of the severity of disease, treatment, and the characteristics of patients. *Clin Infect Dis* 2004; 39: 1783–1790.
9. Shindo Y, Sato S, Maruyama E, *et al.* Implication of clinical pathway care for community-acquired pneumonia in a community hospital: early switch from an intravenous beta-lactam plus a macrolide to an oral respiratory fluoroquinolone. *Intern Med Tokyo Jpn* 2008; 47: 1865–1874.
10. Menéndez R, Martinez R, Reyes S, *et al.* Stability in community-acquired pneumonia: one step forward with markers? *Thorax* 2009; 64: 987–992.
11. Halm EA, Fine MJ, Kapoor WN, *et al.* Instability on hospital discharge and the risk of adverse outcomes in patients with pneumonia. *Arch Intern Med* 2002; 162: 1278–1284.
12. Aliberti S, Zanaboni AM, Wiemken T, *et al.* Criteria for clinical stability in hospitalised patients with community-acquired pneumonia. *Eur Respir J* 2013; 42: 742–749.
13. Bellelli G, Guerini F, Cerri AP, *et al.* A sudden decline in mobility status as an early sign of acute infection in elderly patients: evidence from three case reports. *Aging Clin Exp Res* 2012; 24: 281–284.
14. Viale P, Scudeller L, Petrosillo N, *et al.* Clinical stability in human immunodeficiency virus-infected patients with community-acquired pneumonia. *Clin Infect Dis* 2004; 38: 271–279.
15. Ramirez JA. Clinical stability and switch therapy in hospitalised patients with community-acquired pneumonia: are we there yet? *Eur Respir J* 2012; 41: 5–6.
16. Mikuła T, Cianciara J, Wiercińska-Drapało A. Is there any influence of immune deficit on procalcitonin results? *Hum Immunol* 2011; 72: 1194–1197.
17. Bele N, Darmon M, Coquet I, *et al.* Diagnostic accuracy of procalcitonin in critically ill immunocompromised patients. *BMC Infect Dis* 2011; 11: 224.
18. Griffin AT, Peyrani P, Wiemken T, *et al.* Macrolides *versus* quinolones in *Legionella* pneumonia: results from the Community-Acquired Pneumonia Organization international study. *Int J Tuberc Lung Dis* 2010; 14: 495–499.
19. Arnold FW, Brock GN, Peyrani P, *et al.* Predictive accuracy of the pneumonia severity index *vs* CRB-65 for time to clinical stability: results from the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study. *Respir Med* 2010; 104: 1736–1743.
20. Christensen D, Feldman C, Rossi P, *et al.* HIV infection does not influence clinical outcomes in hospitalized patients with bacterial community-acquired pneumonia: results from the CAPO international cohort study. *Clin Infect Dis* 2005; 41: 554–556.
21. Pereira JM, Paiva JA, Rello J. Severe sepsis in community-acquired pneumonia – early recognition and treatment. *Eur J Intern Med* 2012; 23: 412–419.
22. Ramirez JA, Bordon J. Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic community-acquired *Streptococcus pneumoniae* pneumonia. *Arch Intern Med* 2001; 161: 848–850.
23. Siegel RE. Time to clinical stability for patients with community-acquired pneumonia. *JAMA* 1999; 281: 231–232.
24. Rhew DC, Riedinger MS, Sandhu M, *et al.* A prospective, multicenter study of a pneumonia practice guideline. *Chest* 1998; 114: 115–119.
25. Aliberti S, Peyrani P, Filardo G, *et al.* Association between time to clinical stability and outcomes after discharge in hospitalized patients with community-acquired pneumonia. *Chest* 2011; 140: 482–488.
26. Schuetz P, Müller B, Christ-Crain M, *et al.* Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev* 2012; 9: CD007498.
27. Arancibia F, Ewig S, Martinez JA, *et al.* Antimicrobial treatment failures in patients with community-acquired pneumonia: causes and prognostic implications. *Am J Respir Crit Care Med* 2000; 162: 154–160.
28. Menéndez R, Torres A, Zalacaín R, *et al.* Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. *Thorax* 2004; 59: 960–965.
29. Rosón B, Carratalà J, Fernández-Sabé N, *et al.* Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. *Arch Intern Med* 2004; 164: 502–508.

30. Hoogewerf M, Oosterheert JJ, Hak E, *et al.* Prognostic factors for early clinical failure in patients with severe community-acquired pneumonia. *Clin Microbiol Infect* 2006; 12: 1097–1104.
31. Kaye KS, Harris AD, McDonald JR, *et al.* Measuring acceptable treatment failure rates for community-acquired pneumonia: potential for reducing duration of treatment and antimicrobial resistance. *Infect Control Hosp Epidemiol* 2008; 29: 137–142.
32. Ye X, Sikirica V, Schein JR, *et al.* Treatment failure rates and health care utilization and costs among patients with community-acquired pneumonia treated with levofloxacin or macrolides in an outpatient setting: a retrospective claims database analysis. *Clin Ther* 2008; 30: 358–371.
33. Aliberti S, Amir A, Peyrani P, *et al.* Incidence, etiology, timing, and risk factors for clinical failure in hospitalized patients with community-acquired pneumonia. *Chest* 2008; 134: 955–962.
34. Menéndez R, Cavalcanti M, Reyes S, *et al.* Markers of treatment failure in hospitalised community acquired pneumonia. *Thorax* 2008; 63: 447–452.
35. Hess G, Hill JW, Raut MK, *et al.* Comparative antibiotic failure rates in the treatment of community-acquired pneumonia: results from a claims analysis. *Adv Ther* 2010; 27: 743–755.
36. Ott SR, Hauptmeier BM, Ernen C, *et al.* Treatment failure in pneumonia: impact of antibiotic treatment and cost analysis. *Eur Respir J* 2012; 39: 611–618.
37. Genné D, Sommer R, Kaiser L, *et al.* Analysis of factors that contribute to treatment failure in patients with community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis* 2006; 25: 159–166.
38. Genné D, Kaiser L, Kinge TN, *et al.* Community-acquired pneumonia: causes of treatment failure in patients enrolled in clinical trials. *Clin Microbiol Infect* 2003; 9: 949–954.
39. Jayaprakash B, Varkey V, Anithakumari K. Etiology and clinical outcome of non-resolving pneumonia in a tertiary care centre. *J Assoc Physicians India* 2012; 60: 98–101.
40. Peyrani P, Ramirez J. What is the association of cardiovascular events with clinical failure in patients with community-acquired pneumonia? *Infect Dis Clin North Am* 2013; 27: 205–210.
41. Soto-Gomez N, Anzueto A, Waterer GW, *et al.* Pneumonia: an arrhythmogenic disease? *Am J Med* 2013; 126: 43–48.
42. Corrales-Medina VF, Musher DM, Shachkina S, *et al.* Acute pneumonia and the cardiovascular system. *Lancet* 2013; 381: 496–505.
43. Corrales-Medina VF, Musher DM, Wells GA, *et al.* Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. *Circulation* 2012; 125: 773–781.
44. Oster G, Berger A, Edelsberg J, *et al.* Initial treatment failure in non-ICU community-acquired pneumonia: risk factors and association with length of stay, total hospital charges, and mortality. *J Med Econ* 2013; 16: 809–819.
45. Kyprianou A, Hall CS, Shah R, *et al.* The challenge of nonresolving pneumonia. Knowing the norms of radiographic resolution is key. *Postgrad Med* 2003; 113: 79–82.
46. Kuru T, Lynch JP 3rd. Nonresolving or slowly resolving pneumonia. *Clin Chest Med* 1999; 20: 623–651.
47. Ruiz-González A, Falguera M, Porcel JM, *et al.* C-reactive protein for discriminating treatment failure from slow responding pneumonia. *Eur J Intern Med* 2010; 21: 548–552.
48. Bruns AHW, Oosterheert JJ, Prokop M, *et al.* Patterns of resolution of chest radiograph abnormalities in adults hospitalized with severe community-acquired pneumonia. *Clin Infect Dis* 2007; 45: 983–991.
49. El Solh AA, Aquilina AT, Gunen H, *et al.* Radiographic resolution of community-acquired bacterial pneumonia in the elderly. *J Am Geriatr Soc* 2004; 52: 224–229.
50. Cassiere H, Rodrigues JC, Fein AM. Delayed resolution of pneumonia. When is slow healing too slow? *Postgrad Med* 1996; 99: 151–154.
51. Fein AM, Feinsilver SH. The approach to nonresolving pneumonia in the elderly. *Semin Respir Infect* 1993; 8: 59–72.

Chapter 16

Non-antibiotic therapies for CAP

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SUMMARY: Several novel non-antibiotic therapies have been used in patients with pneumonia. Among many alternatives, anti-inflammatory and immunomodulatory agents such as corticosteroids, statins, nonsteroid anti-inflammatory medications, immunoglobulins and anticoagulants have been tested. Other agents, such as angiotensin-converting enzyme inhibitors and mucolytics, showed a potential beneficial effect on airways protection mechanisms and secretion clearance. The therapeutic effect of nonpharmacological strategies (*i.e.* chest physiotherapy) has also been considered. However, other than use of corticosteroids in certain populations, there is still a need for further research before these medications are recommended for clinical use. This chapter discusses the evidence regarding novel non-antibiotic therapies and the association with clinical outcomes in patients with pneumonia.

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Although antibiotic treatment is the mainstay of management in community-acquired pneumonia (CAP) and is available in all developed countries, pneumonia is still the leading infectious cause of death [1–3]. Much of the mortality and morbidity associated with CAP occurs due to an excessive or damaging host response rather than directly due to infection [4]. An excessive inflammatory response has been considered one of the possible mechanisms [4]. Therefore it has been suggested that strategies aimed at modifying the immune response may be beneficial in CAP. Furthermore, existing therapies that are not part of routine management in CAP, such as antithrombotic agents and chest physiotherapy, have been investigated as possible adjunctive therapies. This overview attempts to assess novel anti-inflammatory strategies, but also evaluates old interventions that may have future potential applications in patients with pneumonia (tables 1 and 2).

Anti-inflammatory and immunomodulatory agents

Corticosteroids

Corticosteroids are anti-inflammatory medications, with multiple uses in clinical practice including treatment of chronic obstructive pulmonary disease (COPD) and asthma [14, 15]. Corticosteroids cause modulation of the exaggerated inflammatory response, which may explain the possible positive effects of corticosteroids in inflammatory/infectious processes such as pneumonia. The addition of a corticosteroid to the antimicrobial therapy in patients with

Table 1. Potential adjunctive therapy in patients with community-acquired pneumonia

Anti-inflammatory
Corticosteroids
Statins
Tissue factor pathway inhibitor
Activated protein C
Aspirin
Immunomodulatory
Statins
Granulocyte colony-stimulating factor
Heparin
Immunoglobulins
Anticoagulation or antithrombotic
Heparin
Activated protein C
Tissue factor pathway inhibitor
Statins
Increased airways protection mechanisms and secretion clearance
Angiotensin-converting enzyme inhibitors
Mucolytics
Chest physiotherapy

Randomised controlled trials investigating these therapies are summarised in table 2.

pneumonia is not currently recommended, despite some promising results showing improved clinical outcomes. Observational studies have suggested a beneficial effect of corticosteroids in patients with pneumonia. GARCIA-VIDAL *et al.* [16] retrospectively evaluated 308 patients with severe pneumonia and found lower mortality among patients treated with systemic corticosteroids in addition to antibiotic treatment (OR 0.28, 95% CI 0.113–0.732). A study by SALLUH *et al.* [17] on mechanically ventilated patients (n=111) with severe pneumonia showed no influence of corticosteroids on intensive care unit (ICU) and hospital mortality, withdrawal of vasopressors, and organ failure recovery. This information contrasts with the evidence suggested by randomised controlled trials (RCTs) that assessed the clinical efficacy of corticosteroids in patients with pneumonia. CONFALONIERI *et al.* [18] tested the clinical efficacy of hydrocortisone in patients with pneumonia requiring ICU admission. Patients treated with hydrocortisone had lower mortality, lower levels of serum C-reactive protein (CRP) and improvement in important clinical end-points, such as chest radiography, multiple organ dysfunction syndrome severity scale, arterial oxygen tension (P_aO_2)/inspiratory oxygen fraction (F_IO_2) ratio, and ICU and hospital stay. After an interim analysis of data from the first 46 patients, enrolment was suspended because of the significant beneficial effects of corticosteroid treatment. However, the small sample size and baseline group differences limited the generalisability of the results. MIKAMI *et al.* [19] performed an open-label RCT with prednisone in 31 hospitalised patients with pneumonia. Prednisone treated patients had an early stability of vital signs and a shorter duration of intravenous antimicrobial therapies. SNIJDERS *et al.* [20] compared prednisolone against placebo in 213 hospitalised pneumonia patients and did not find differences in the rate of 30-day mortality, time to clinically stability or length of hospital stay. However, corticosteroid treated patients had faster decline in serum CRP levels, but more late clinical failures (those that occurred >72 h after admission) compared to placebo treated pneumonia patients. MEIJVIS *et al.* [21] compared intravenous dexamethasone against placebo in patients with pneumonia, and found no differences in in-hospital mortality, ICU admission and severe adverse events. Despite these results, corticosteroid treated patients had a shorter length of hospital stay compared to the placebo group. Another observational study in 56 pneumonia patients admitted to the hospital showed that methylprednisolone in combination with antibiotics was more likely to improve the rate of respiratory failure and the speed of clinical resolution [22].

A meta-analysis by NIE *et al.* [23] concluded that the use of corticosteroids was associated with improved mortality in severe pneumonia patients, particularly among those who received more than 7 days of systemic therapy. This meta-analysis suggested that there was no benefit from corticosteroid use in the treatment of nonsevere CAP patients. However, two other recent meta-analyses concluded that corticosteroids did not significantly alter mortality in pneumonia patients, but could be beneficial for accelerating the time to resolution of symptoms and reducing the length of hospital stay [24, 25]. Therefore, we suggest that despite promising results with the use of

Table 2. Randomised controlled trials investigating adjuvant therapies for community-acquired pneumonia (CAP)

Therapy	First author [ref.]	Trial	Aim	Participants n	Comparison groups	Clinical outcomes reported	Results	Conclusion
Anti-inflammatory and immuno-modulatory agents								
Recombinant tissue factor pathway inhibitor	ABRAHAM [5]	OPTIMIST	To determine if tifacogin provides mortality benefit in patients with severe sepsis and high INR	1987	*i.v.* infusion of tifacogin (0.025 mg·kg^{-1}·h^{-1} for 96 h) *versus* placebo	28-day all-cause mortality	34.2% 28-day mortality in the tifacogin group *versus* 33.9% in the placebo group (p=0.88)	Treatment with tifacogin had no effect on all-cause 28-day mortality in patients with severe sepsis and high INR
	WUNDERINK [6]	CAPTIVATE	To evaluate the impact of adjunctive tifacogin on mortality in patients with severe CAP	1864	Continuous *i.v.* infusion of tifacogin (0.025 mg·kg^{-1}·h^{-1} for 96 h) *versus* placebo	Severity-adjusted 28-day all-cause mortality	28-day mortality rates were similar between the tifacogin (18%) and placebo groups (17.9%) (p=0.56)	Tifacogin showed no mortality benefit in patients with severe CAP
Recombinant human activated protein C	BERNARD [7]	PROWESS	To assess if treatment with drotrecogin alfa activated reduced the rate of death in patients with severe sepsis	1690	Drotrecogin alfa activated (24 µg per kg of body weight per hour for 96 h) *versus* placebo	28-day all-cause mortality	Mortality rate was 30.8% in the placebo and 24.7% in the drotrecogin alfa activated group (p=0.005)	Treatment with drotrecogin alfa activated significantly reduces mortality in patients with severe sepsis
	RANIERI [8]	PROWESS-SHOCK	To assess if treatment with drotrecogin alfa activated reduced the rate of death in patients with septic shock	1697	Drotrecogin alfa activated (24 µg per kg of body weight per hour for 96 h) *versus* placebo	Primary outcome: any cause 28-day mortality. Secondary outcome: any cause 90-day mortality	At 28 days, 26.4% patients in the drotrecogin alfa activated and 24.2% in the placebo group died (p=0.31) At 90 days, 34.1% in the drotrecogin alfa activated and 32.7% in the placebo group died (p=0.56)	Drotrecogin alfa activated did not significantly reduce mortality at 28- or 90-days in patients with septic shock
Ibuprofen	BERNARD [9]	IBUPROFEN IN SEPSIS	To assess the role of ibuprofen in patients with sepsis	455	*i.v.* ibuprofen (10 mg per kg of body weight[#] given every 6 h for eight doses) *versus* placebo	30-day mortality Incidence and duration of shock and ARDS	Ibuprofen did not reduce the incidence or duration of shock or ARDS 30-day survival did not significantly improve (mortality 37% with ibuprofen *versus* 40% with placebo)	In patients with severe sepsis, ibuprofen does not prevent the development of shock or ARDS and does not improve survival
Aspirin	OZ [10]		To test the hypothesis that aspirin would reduce the risk for ACS in patients with CAP	185	Aspirin (300 mg daily for 1 month) *versus* control group (no aspirin)	Primary outcome: occurrence of ACS within 1 month of admission Secondary outcomes: 1-month any-cause and CV death	Rates of ACS at 1 month were 1.1% in the aspirin group and 10.6% in the control group (p=0.015) There was no significant decrease in the risk of death from any cause (p=0.15), but the aspirin group had a decreased risk of CV death (p= 0.044)	Aspirin is beneficial in the reduction of ACS and CV mortality among patients with CAP

Table 2. Continued

Therapy	First author [ref.]	Trial	Aim	Participants n	Comparison groups	Clinical outcomes reported	Results	Conclusion
Statins	KRUGER [11]	ANZICS	To test whether atorvastatin affects biological and clinical outcomes in patients with severe sepsis	250	Atorvastatin (20 mg daily) *versus* matched placebo	Primary outcome: plasma IL-6 levels Secondary outcomes: modification of SOFA scores, LOS, and ICU, hospital, 28- and 90-day mortality	No difference in IL-6 concentrations between atorvastatin and placebo Baseline plasma IL-6 was significantly lower among previous statin users No difference in LOS, SOFA scores or mortality. Among prior statin users those randomised to placebo had a greater 28-day mortality	Atorvastatin in severe sepsis did not affect IL-6 levels Prior statin use was associated with a lower baseline IL-6 levels and continuation of atorvastatin in this cohort was associated with improved 28-day survival
	PATEL [12]	ASEPSIS	To determine if atorvastatin reduces sepsis progression in statin naïve patients hospitalised with sepsis	100	Atorvastatin (40 mg daily) *versus* placebo	Primary outcome: rate of sepsis progressing to severe sepsis Secondary outcomes: ICU admission rate, 28-day and 1-year hospital readmission rate, hospital LOS, and 28-day and 1-year hospital mortality	Patients in the atorvastatin group had a significantly lower conversion rate to severe sepsis compared to placebo (4% *versus* 24% p= 0.007) No significant difference in length of hospital stay, ICU admissions, 28-day and 12-month readmissions or mortality was observed	Acute administration of atorvastatin in patients with sepsis may prevent sepsis progression
Anticoagulants and antithrombotic agents								
Unfractionated heparin	JAIMES [13]	HETRASE TRIAL	To evaluate the effect of heparin on septic patients	319	Unfractioned heparin (500 units per hour for 7 days) *versus* placebo	Primary outcome: LOS and change from baseline MODS score. Secondary outcomes: 28-day all-cause mortality	Median LOS 12.5 days for placebo *versus* 12 days in the heparin group (p= 0.98) MODS score improved equally in the two groups (p= 0.240) 16% 28-day mortality for placebo *versus* 14% in the heparin group (p=0.65)	No beneficial effect of heparin on the chosen primary outcomes or in the 28-day mortality rate

INR: international normalised ratio; ARDS: acute respiratory distress syndrome; ACS: acute coronary syndromes; CV: cardiovascular; ANZICS: Australian and New Zealand Intensive Care Society; IL: interleukin; SOFA: sequential organ failure assessment; LOS: length of stay; ICU: intensive care unit; MODS: multiple organ dysfunction syndrome. #: maximal dose 800 mg.

corticosteroids for patients with pneumonia, further RCTs are needed to define if this intervention should be adopted in clinical practice.

Statins

Statins are well known regulators of cholesterol metabolism and have proven to be useful for protection from cardiovascular events [26, 27]. They also seem to have anti-inflammatory and immunoregulatory properties, which have been investigated in patients with sepsis and pneumonia [28]. Some mechanisms advocated for the anti-inflammatory effect of statins include antioxidant, anti-apoptotic and antithrombotic activity [26]. A recent meta-analysis investigating the immunomodulatory effects of statins in CAP reported modulation of neutrophil function and reduction of cytokine expression and cytokine release as possible mechanisms [29].

Despite the lack of data from RCTs, a large number of observational studies have been published on the use of statins for the treatment of sepsis or pneumonia [28]. The majority of the studies suggest that statins may have a positive role in prevention and treatment of patients with sepsis and/or pneumonia [30]. Patients who were taking statins at the time of development of pneumonia or another infection were less likely to develop sepsis, death from sepsis or complications leading to ICU admission [31]. A meta-analysis by TLEYJEH *et al.* [32] evaluated nine studies that addressed the role of statins in treating infections, including bacteraemia, pneumonia and sepsis. The analysis suggested an improvement in the chance of short-term survival (in-hospital up to 30 days) in favour of statins (pooled adjusted effect estimate of 0.55, 95% CI 0.36–0.83).

However, at least two main objections have been raised to these promising results. First, the majority of the observational studies performed, to date, have the limitations and potential biases of retrospective studies. Second, all patients were already receiving statin treatment at the time of pneumonia development [31]. Furthermore, despite finding an overall protective effect of statins on 30-day mortality, a recent meta-analysis reported that this effect weakened after correction for important confounders, such as vaccination status [33]. Notably, no effect of statins on mortality after pneumonia was observed when only prospective cohort studies were considered.

Prospective cohort studies showed contradicting results and cast new light on the role of statins in patients with pneumonia [34–36]. The authors of the studies that found no evidence for a protective effect of statins on pneumonia speculated that previous reports describing a benefit of statins may have been biased by the healthy user effect (the propensity for patients who receive one preventive therapy to adopt other healthy behaviours) [37]. In view of these considerations, conclusions on this important topic should await the results of RCTs on patients with pneumonia.

Two recent RCTs have tested the role of statins in patients with sepsis. In a multicentre double-blind RCT, KRUGER *et al.* [11] randomised 250 ICU patients with severe sepsis to either atorvastatin (20 mg daily) or matched placebo (Australian and New Zealand Intensive Care Society trial). No difference was found between the groups in length of stay, mortality at ICU or hospital discharge, or 28- or 90-day mortality. Interestingly, when considering only the 77 patients with prior statin use, those randomised to placebo had a greater 28-day mortality compared with those who received atorvastatin (28% *versus* 5%, p=0.01). This difference was not statistically significant at 90 days (28% *versus* 11%, p=0.06). Furthermore, patients with prior statin use had lower baseline interleukin-6 levels. Evidence from this study suggests that there is no benefit in starting treatment with statins during hospitalisation for a severe infectious disease. However, there is benefit in continuing statin therapy during hospitalisation in prior users.

In the ASEPSIS trial PATEL *et al.* [12] randomised 100 statin naïve patients with sepsis to 40 mg atorvastatin daily or placebo for the duration of their hospital stay. Patients in the atorvastatin group had a significantly lower rate of conversion to severe sepsis (onset of one or more organ dysfunctions) compared to placebo (4% *versus* 24% p=0.007). However, no significant differences

in length of hospital stay, number of ICU admissions, 28-day and 12-month readmissions or mortality were observed.

Statins have a protective role on cardiovascular events. Recent literature has suggested that cardiovascular events are one of the most common complications developed by CAP patients [38]. Pneumonia-induced changes, such as hypoxaemia, systemic inflammatory response and procoagulant state, may act as a trigger in patients at risk [39]. In this scenario, use of statins, both prior to and during hospitalisation, becomes important in patients with CAP that also have an increased cardiovascular risk. Acting either as plaque stabilisers or anti-inflammatory agents, statins may prevent acute cardiovascular events and cardiovascular deaths in this group of patients.

Therefore, we suggest continuing statin treatment in patients with CAP and high cardiovascular risk. Further RCTs are needed to determine the impact of statins at admission for pneumonia, particularly among patients without risk-factors for coronary artery disease or other indications for statins use.

Tissue factor pathway inhibitor

Tissue factor pathway inhibitor (TFPI) is a protein with anticoagulant action through direct inhibition of coagulation factors, such as factor Xa. In addition, TFPI also has anti-inflammatory properties, most likely through its ability to limit thrombin generation and, thereby, the proinflammatory intracellular signalling mediated through activation of protease-activated receptors [40]. VAN DEN BOOGAARD *et al.* [41] examined the effect of recombinant human TFPI (rhTFPI) on inflammation and bacterial outgrowth in *Streptococcus pneumoniae* pneumonia in mice. They found that rhTFPI inhibited accumulation of neutrophils in lung tissue and reduced the levels of several cytokines and chemokines in lungs and plasma, but these effects became evident only in the absence of concurrent antibiotic treatment.

TFPI has been used in RCTs as a treatment for severe sepsis. The OPTIMIST trial on severe sepsis patients did not show any difference in overall 28-day mortality rate in the rhTFPI (tifacogin) treatment group compared to the placebo group [5]. Subgroup analysis revealed that, in patients with severe CAP, there was a trend toward improved survival in the rhTFPI treatment group over the placebo group. This survival trend became statistically significant when subgroup analysis was limited to patients not treated with heparin in whom an infectious organism was identified [42].

Given these results, WUNDERINK *et al.* [6] performed a multicentre, double-blind RCT to evaluate the impact of adjunctive rhTFPI on mortality in patients with severe CAP (CAPTIVATE trial) [6]. In the 2138 randomised patients, the 28-day all-cause mortality rates were similar between the rhTFPI (0.025 $mg \cdot kg^{-1} \cdot h^{-1}$ continuous intravenous infusion over 96 h) and the placebo groups (18% *versus* 17.9%, p=0.56). The incidence of adverse events was comparable between the two groups. Therefore, given the results of these well-designed RCTs, the use of rhTFPI (tifacogin) is currently not recommended in the treatment of patients with severe CAP.

Activated protein C

Activated protein C (drotrecogin alfa) has anticoagulant and possibly anti-inflammatory activities [43], similar to TFPI. Therefore, it has been evaluated in 1690 patients with severe sepsis in a double-blind RCT (the PROWESS (Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial) [7]. This trial showed an absolute risk reduction in 28-day mortality in patients treated with activated protein C compared to the placebo group (24.7% *versus* 30.8%, p=0.005). However, the group of patients treated with activated protein C showed a trend towards increased incidence of serious bleeding compared to the placebo group (3.5% *versus* 2.0%, p=0.06). A subsequent retrospective subgroup analysis of severe CAP patients from the PROWESS trial showed that patients treated with activated protein C had a relative risk reduction of 28% for 28-day mortality and of 14% for 90-day mortality [44]. The survival benefit was most pronounced in severe CAP patients with *S. pneumoniae* and in severe CAP patients at

high risk of death (calculated by severity scores). A recent multicentre double-blind RCT (the PROWESS-SHOCK trial) assigned 1697 patients with septic shock to receive either activated protein C (at a dose of 24 $\mu g \cdot kg^{-1} \cdot h^{-1}$) or placebo for 96 h [8]. No differences were found between the two groups in the primary outcomes (28- and 90-day mortality).

Given the paucity of the studies and the controversial results obtained, recombinant human activated protein C was withdrawn from the market and is no longer an option for the treatment of severe sepsis or severe CAP patients.

Antiplatelet and nonsteroidal anti-inflammatory agents

Platelets play an important role in inflammation, releasing mediators responsible for immune cell activation and recruitment, and in the coagulation cascade, which is one of the possible steps in the development of acute coronary syndromes. Recent data emphasise the high rate of cardiovascular events among pneumonia patients [38, 39]. Pneumonia may trigger cardiovascular events as a result of inflammatory reactions and prothrombotic changes. In this setting, the anti-aggregating and anti-inflammatory properties of aspirin may play a preventive role. OZ *et al.* [10] randomised 185 patients with pneumonia to aspirin (300 mg daily for 1 month) plus standard care or standard care alone. The authors found that aspirin was associated with a 9% absolute reduction in the risk for acute cardiovascular events within 1 month. There was no significant decrease in the risk of 28-day any-cause mortality, but the aspirin group had a decreased risk of 28-day cardiovascular mortality. In another study on 127 elderly patients with severe CAP, WINNING *et al.* [45] reported that 40 patients on antiplatelet drugs at the time of admission (the most common one was low dose aspirin (84% of patients)) had less need for ICU admission (OR 0.32, 95% CI 0.04–0.87) and shorter length hospital of stay (13.9 days *versus* 18.2 days, $p<0.02$) when compared to those not taking these drugs. GROSS *et al.* [46] retrospectively investigated the effect of clopidogrel on the incidence and severity of CAP. The authors found that clopidogrel was associated with increased CAP incidence, but it did not increase severity among inpatients. However, since this study was retrospective and could not quantify all variables (*e.g.* aspirin use) the role of clopidogrel should be further explored.

Other studies have been performed on nonsteroidal anti-inflammatory drugs (NSAIDs). A few authors have described an improvement in gas exchange as a result of NSAID use in patients with sepsis or pneumonia [9, 47]. A possible explanation for this finding is the reduction of the intrapulmonary shunt fraction [48]. BERNARD *et al.* [9] conducted a randomised, double-blind, placebo-controlled trial of intravenous ibuprofen (10 mg per kilogram of body weight (maximal dose 800 mg), given every 6 h for eight doses) in 455 patients with sepsis. The authors found that treatment with ibuprofen did not reduce the incidence or duration of shock or acute respiratory distress syndrome (ARDS) and did not significantly improve the rate of 30-day survival. VOIRIOT *et al.* [49] performed a study on 90 consecutive patients with CAP admitted to the ICU, of which 32 (36%) received NSAIDs prior to hospital referral. Compared with non-exposed patients, they were younger and had fewer comorbidities but similar severity of disease at presentation, despite a longer duration of symptoms. However, NSAID treated patients were more likely to develop pleuropulmonary complications, such as pleural empyema and lung cavitation (37.5% *versus.* 7% $p=0.0009$). Even after multivariable analyses, NSAID exposure was independently associated with the occurrence of pleuropulmonary complications (OR 8.1, 95% CI 2.3–28). The authors concluded that NSAID exposure in the early stage of CAP was associated with a more complicated course but a blunted systemic inflammatory response, which might have been associated with a late diagnosis, a delay in seeking medical attention and a prolonged course.

In a recent review CORRALES-MEDINA *et al.* [50] suggest considering the use of aspirin in patients with high risk of pneumonia who otherwise have an indication for it; furthermore, it may also be reasonable to consider its routine use in treating pneumonia in non-critically ill patients with significant coronary risk factors. However, given the conflicting data (protective effect of aspirin on cardiovascular complications, but possible negative effect of NSAIDs on pleuropulmonary

complications), we do not recommend the use of NSAIDs in patients with pneumonia, and more studies are needed to evaluate the efficacy of aspirin.

Granulocyte colony-stimulating factor

The association between white blood cells and pneumonia has been well known for centuries, recognising that leukocytosis and neutrophilia are markers of infection. Colony-stimulating factors are a family of acidic glycoproteins that are required for the proliferation and differentiation of haematopoietic progenitor cells [51]. Granulocyte colony-stimulating factor (G-CSF) is a naturally occurring cytokine, which may augment the neutrophil response to bacterial infections. In addition to its value in the management of haematological malignancies and in the treatment of chemotherapy-induced neutropenia, recombinant G-CSF has been suggested as an adjuvant treatment for patients with pneumonia and sepsis [52–55]. The use of G-CSF in non-neutropenic bacterial infection is based on the possible mechanisms of action. The first possible mechanism is the enhancement of chemotaxis, superoxide production and bacterial killing activity. The second is by exerting immunomodulation of the cytokine response in patients with sepsis. And the third is a possible increase in intracellular uptake of antibiotics. However, despite the encouraging preclinical studies that suggested potential therapeutic value, the clinical results have been disappointing. The Cochrane collaboration performed a systematic review and meta-analysis of RCTs in patients hospitalised with CAP or hospital-acquired pneumonia [52]. Six studies identified in 2018 patients showed that G-CSF was safe but had no effect on improving 28-day mortality [52]. In addition, there were no increases in serious adverse events and organ dysfunction associated with the administration of G-CSF. Therefore, there is no evidence suggesting that G-CSF should be used for the treatment of pneumonia. However, it is possible that G-CSF could potentially have a benefit in patients with pneumonia if administered prophylactically or earlier in the process. Careful consideration should be placed on patients with sepsis due to the risk of adverse events, particularly the development of ARDS.

Immunoglobulins

Polyclonal intravenous immunoglobulin therapy is currently used in patients with immunosuppression due to immunoglobulin deficiencies and in patients with autoimmune disorders, including autoimmune neuropathies (*e.g.* Guillain–Barré Syndrome) [56]. In the pre-antibiotic era it was used with success, in the form of passive immunisation with serum, in patients with pneumonia [31].

No studies have evaluated the efficacy of polyclonal intravenous immunoglobulin therapy in patients with CAP after the advent of antibiotic therapy. However, two meta-analyses published in 2007 evaluated the effect of polyclonal intravenous immunoglobulin therapy on mortality in critically ill adult patients with severe sepsis [57, 58]. LAUPLAND *et al.* [57] reported an overall reduction in mortality with the use of polyclonal intravenous immunoglobulin in adults with severe sepsis and septic shock, although significant heterogeneity existed among the included trials and this result was not confirmed when only high-quality studies were analysed. TURGEON *et al.* [58] observed a survival benefit for patients with sepsis who received polyclonal intravenous immunoglobulin therapy compared with those who received placebo or no intervention (risk ratio 0.74, 95% CI 0.62–0.89). However, most of the trials considered in the analysis were published before the introduction of new developments that modified the care and outcomes of critically ill patients with sepsis, including early goal-directed therapy [59].

Given these data, no conclusions can be made and future RCTs should address the real therapeutic effect of polyclonal intravenous immunoglobulin in both pneumonia and severe sepsis patients.

Anticoagulants and antithrombotic agents

Prophylactic administration of anticoagulants is recommended for patients at high risk of venous thromboembolism (Padua score $\geqslant 4$ or critically ill) [60]. In 2001, DEAN *et al.* [61] demonstrated

that the implementation of a protocol, which included timely administration of antibiotics and unfractionated heparin, reduced the 30-day mortality in a group of 28 661 non-septic patients with CAP. Results from a meta-analysis based on animal data suggest a potentially life-saving effect of heparin used as an immunomodulatory agent for the treatment of patients with sepsis [62]. However, a randomised, double-blind, placebo-controlled, single-centre clinical trial (the HETRASE study) that compared unfractionated heparin (500 units per hour for 7 days) *versus* placebo in 319 patients with sepsis found no difference in length of stay and 28-day mortality rate between the two groups [13].

Anticoagulants have also been tested in a nebulised form. A recent review by TUINMAN *et al.* [63] evaluated the role of different nebulised anticoagulants (activated protein C, antithrombin, heparin and danaparoid) in animals and humans with acute lung injury (ALI). Although nebulisation of anticoagulants seemed to attenuate pulmonary coagulopathy and frequently also inflammation in preclinical studies, data from human trials were too limited to reach a conclusion. It is noteworthy that danaparoid and heparin, even in a nebulised form, seem to affect systemic coagulation.

Therefore, we recommend the use of systemic anticoagulants (*e.g.* low molecular weight heparin, unfractionated heparin or fondaparinux) in hospitalised patients at high risk of venous thromboembolism and without risk of bleeding. However, the role of anticoagulants in modulating lung inflammation and improving ALI in patients with CAP is not yet clear and needs to be addressed in future clinical trials.

Agents that increase airways protection mechanisms and secretion clearance

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Angiotensin-converting enzyme inhibitors (ACEIs) increase cough reflex and improve swallowing and, therefore, they have been advocated to prevent silent aspiration of oropharyngeal pathogens. These properties may ultimately decrease the risk of CAP, in particular aspiration pneumonia [43, 64]. Despite this, a recent systematic review on risk factors for aspiration pneumonia in frail older patients listed angiotensin I-converting enzyme deletion/deletion genotype and ACEI use as significant risk factors for aspiration [65].

Several studies have reported an association between ACEI use and decreased risk of developing CAP or better clinical outcomes (*e.g.* decreased mortality risk) in patients with CAP [4], especially in post-stroke patients [66, 67] and Asian cohorts [68, 69]. Other studies performed on large cohorts of predominantly white patients with CAP found mixed results for the association of ACEIs and clinical outcomes [70, 71]. Part of the discrepancy may be caused by the different classes of ACEIs used. The risk of developing CAP may be greater for lipophilic ACEIs (*e.g.* fosinopril and quinapril) compared with hydrophilic ACEIs (*e.g.* captopril, enalapril and lisinopril) [72, 73].

Similar to ACEIs, angiotensin receptor blockers (ARBs) reduce angiotensin II action. However, the role pf ARBs in pneumonia prevention is much less evident than that of ACEIs. A recent meta-analysis by CALDEIRA *et al.* [74] evaluated the incidence of pneumonia and pneumonia-related mortality in patients on ACEI and ARB therapy. The authors found that ACEIs were associated with a significantly reduced risk of pneumonia compared with both control treatment (OR 0.66, 95% CI 0.55–0.80) and ARBs (OR 0.70, 95% CI 0.56–0.86). The risk of pneumonia did not differ between patients who did or did not use ARBs (OR 0.95, 95% CI 0.87–1.04). Compared with control treatments, both ACEIs (OR 0.73, 95% CI 0.58–0.92) and ARBs (OR 0.63, 95% CI 0.40–1.00) were associated with a decrease in pneumonia-related mortality, without differences between interventions. However, a possible bias of this meta-analysis is that most of the studies included did not consider pneumonia development as a primary outcome and in several studies pneumonia

incidents were compiled from reported adverse events [75]. MORTENSEN *et al.* [76] conducted a retrospective study to evaluate the effect of ACEI and ARB therapy on pneumonia-related outcomes in patients aged ⩾65 years hospitalised for pneumonia. The authors found that prior (OR 0.88, 95% CI 0.80–0.97) and inpatient (OR 0.58, 95% CI 0.48–0.69) ACEIs use, as well as prior (OR 0.73, 95% CI 0.58–0.92) and inpatient ARBs use (OR 0.47, 95% CI 0.30–0.72) were associated with decreased mortality. LIU *et al.* [67] performed a study on the effect of ACEIs and ARBs on pneumonia hospitalisation in patients with stroke history in Taiwan. ACEIs use was associated with a decreased pneumonia risk (OR 0.70, 95% CI 0.68–0.87) and a significant dose–response relationship ($p<0.01$), but ARBs use did not modify pneumonia risk (OR 1.02; 95% CI 0.87–1.19).

Therefore, current evidence does not justify initiation of treatment with ACEIs in patients with pneumonia. However, for two subgroups, patients of Asian origin and post-stroke patients, the evidence of a benefit from ACEIs (specifically, hydrophilic ACEIs) use on pneumonia prevention is stronger. Based on this evidence, in guidelines published in 2009 the Japanese Society of Hypertension suggested that ACEIs should be the treatment of choice for patients with hypertension that repeatedly develop aspiration pneumonia [77].

No conclusions can be made on ARBs use and pneumonia. Current evidence does not show a benefit of ARBs use on pneumonia prevention, despite a possible protective effect on outcomes (reduced pneumonia-related mortality). This lack of effect on pneumonia risk may be explained by the fact that this class of drugs does not increase cough reflex. Future RCTs should address the effect of ACEIs and ARBs on pneumonia.

Over-the-counter medications

Over-the-counter medications, including antitussives, expectorants, mucolytics, antihistamine-decongestants and histamine H1 receptor antagonists, are used as symptom relievers in patients with cough and sputum production due to upper respiratory tract infections. In a recent meta-analysis regarding over-the-counter medications to reduce cough as an adjunctive therapy in children and adults with pneumonia, mucolytics were found to be potentially beneficial, but there was insufficient evidence to recommend them as an adjunctive treatment for pneumonia [78]. Therefore, no recommendations can be made about over-the-counter medications for cough in pneumonia patients. Future studies are warranted to better clarify this topic.

Chest physiotherapy

Chest physiotherapy consists of a variety of techniques that mainly aim at improving secretion clearance. These techniques have been extensively studied in patients with chronic airway diseases that cause chronic sputum production, such as bronchiectasis and severe COPD. In acute diseases, such as pneumonia, the rationale for using chest physiotherapy is mainly gas exchange improvement.

A recent meta-analysis by YANG *et al.* [79] evaluated the role of chest physiotherapy in patients with pneumonia. Six RCTs, involving a total of 434 participants, were included and four types of chest physiotherapy were considered: conventional chest physiotherapy; osteopathic manipulative treatment; active cycle of breathing techniques; and positive expiratory pressure. None of the techniques considered proved to influence the primary outcomes (mortality and cure rate). Osteopathic manipulative treatment (*versus* placebo) and positive expiratory pressure (*versus* no physiotherapy) reduced the mean duration of hospital stay by 2 days. However, all the results of studies on chest physiotherapy had limitations intrinsic to the type of intervention. Physiotherapy efficacy depends on the skill of the care giver and comparisons are difficult in techniques that are not completely standardised [80]. Furthermore, given the operator-dependence of these techniques, a good quality double-blind RCT is very difficult to achieve.

Patients with severe pneumonia causing respiratory failure and, thus, requiring ventilatory support may be the group that most benefit from chest physiotherapy. Two recent small studies on mechanically ventilated patients admitted to the ICU reported an increased rate of successful

weaning trials in patients treated with chest physiotherapy [81, 82]. However, a systematic review published by STILLER [83] in 2013 evaluating the effectiveness of physiotherapy in ICU patients reported conflicting data regarding the routine use of multimodality respiratory physiotherapy. In particular, while there is strong evidence to support the use of respiratory therapist-driven weaning protocols, further studies with larger sample sizes are needed to evaluate the effectiveness of most of the other physical therapies [84].

Aside from intubated patients, other special groups of patients might particularly benefit from chest physiotherapy; for instance, those with impaired cough reflex or compromised respiratory muscle function, such as neuromuscular and neurological patients [80]. These patients might benefit from chest physiotherapy as a rehabilitation technique, even out of the acute phase [85].

In conclusion, chest physiotherapy may be prescribed for patients with CAP, especially those with hypersecretion or other predisposing conditions, such as neuromuscular, neurological and chronic airway diseases that impair secretion clearance mechanisms [43, 86]. Mechanically ventilated patients are also potential candidates for chest physiotherapy, but further research is warranted before making strong recommendations.

Other agents

β_2-agonists

No clinical trials have been performed to investigate the role of β_2-agonists as an adjunctive therapy in patients with CAP. However, the role of β_2-agonists has been evaluated in animal models with pneumonia. ROBRIQUET *et al.* [87] investigated the effects of terbutaline on lung permeability and alveolar fluid clearance in rats with acute *Pseudomonas aeruginosa* pneumonia causing acute lung injury. β_2-agonists exerted a beneficial effect on lung fluid balance and alveolar oedema formation, by reducing pulmonary endothelial permeability and increasing alveolar fluid clearance. SU *et al.* [88] tested the effects of β-adrenoceptor inhibition in mice with acute *Escherichia coli* pneumonia. Endogenous β-adrenoceptor tone seems to have a protective effect in limiting accumulation of extravascular lung water by reducing lung vascular injury and alveolar oedema.

On the basis of these data, no recommendations can be made regarding β_2-agonist use in patients with pneumonia. Future studies are warranted to explore the possible therapeutic benefits.

Inhaled nitric oxide

The rationale for utilisation of nitric oxide originated from *in vitro* observations of its bactericidal properties. Studies in animal models, such as rats with *P. aeruginosa* pneumonia [89–91], showed that bacterial loads decreased with inhaled nitric oxide, therefore suggesting a potential therapeutic effect in patients with pneumonia and cystic fibrosis. Inhaled nitric oxide has also been recently tested in eight patients with unilateral pneumonia and hypoxaemia [92]. The rationale of the intervention is the selective pulmonary vasodilator property of nitric oxide, which may improve pulmonary gas exchange by increasing intrapulmonary shunt. Compared with patients at baseline, low doses of inhaled nitric oxide caused a significant dose-dependent fall in pulmonary vascular resistance and improvement of P_{aO_2}.

Future studies and RCTs should address the potential therapeutic effect of nitric oxide in patients with pneumonia.

Conclusions

Adjunctive non-antibiotic therapies, directed at the host response rather than the pathogens, have been tested in order to improve clinical outcomes in patients with CAP. Corticosteroids, statins,

ACEIs and anticoagulants have been used with some encouraging results, but data are still too scarce to recommend these agents for routine use. Future studies should address the impact of these medications on the main clinical outcomes in CAP patients, particularly those with severe pneumonia.

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Statement of Interest

None declared.

References

1. Jemal A, Ward E, Hao Y, *et al.* Trends in the leading causes of death in the United States, 1970–2002. *JAMA* 2005; 294: 1255–1259.
2. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997; 349: 1498–1504.
3. Heron M, Hoyert DL, Murphy SL, *et al.* Deaths: final data for 2006. *Natl Vital Stat Rep* 2009; 57: 1–134.
4. Sibila O, Restrepo MI, Anzueto A. What is the best antimicrobial treatment for severe community-acquired pneumonia (including the role of steroids and statins and other immunomodulatory agents). *Infect Dis Clin North Am* 2013; 27: 133–147.
5. Abraham E, Reinhart K, Opal S, *et al.* Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. *JAMA* 2003; 290: 238–247.
6. Wunderink RG, Laterre P-F, Francois B, *et al.* Recombinant tissue factor pathway inhibitor in severe community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2011; 183: 1561–1568.
7. Bernard GR, Vincent JL, Laterre PF, *et al.* Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344: 699–709.
8. Ranieri VM, Thompson BT, Barie PS, *et al.* Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 2012; 366: 2055–2064.
9. Bernard GR, Wheeler AP, Russell JA, *et al.* The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. *N Engl J Med* 1997; 336: 912–918.
10. Oz F, Gul S, Kaya MG, *et al.* Does aspirin use prevent acute coronary syndrome in patients with pneumonia: multicenter prospective randomized trial. *Coron Artery Dis* 2013; 24: 231–237.
11. Kruger P, Bailey M, Bellomo R, *et al.* A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. *Am J Respir Crit Care Med* 2013; 187: 743–750.
12. Patel JM, Snaith C, Thickett DR, *et al.* Randomized double-blind placebo-controlled trial of 40 mg/day of atorvastatin in reducing the severity of sepsis in ward patients (ASEPSIS Trial). *Crit Care* 2012; 16: R231.
13. Jaimes F, De La Rosa G, Morales C, *et al.* Unfractioned heparin for treatment of sepsis: a randomized clinical trial (The HETRASE Study). *Crit Care Med* 2009; 37: 1185–1196.
14. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. GINA, 2012. www.ginasthma.org/documents/4 Date last updated: December 2012. Date last accessed: January 13, 2014.
15. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. GOLD, 2013. www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html Date last updated: February 2013. Date last accessed: January 13, 2014.
16. Garcia-Vidal C, Calbo E, Pascual V, *et al.* Effects of systemic steroids in patients with severe community-acquired pneumonia. *Eur Respir J* 2007; 30: 951–956.
17. Salluh JIF, Soares M, Coelho LM, *et al.* Impact of systemic corticosteroids on the clinical course and outcomes of patients with severe community-acquired pneumonia: a cohort study. *J Crit Care* 2011; 26: 193–200.
18. Confalonieri M, Urbino R, Potena A, *et al.* Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med* 2005; 171: 242–248.
19. Mikami K, Suzuki M, Kitagawa H, *et al.* Efficacy of corticosteroids in the treatment of community-acquired pneumonia requiring hospitalization. *Lung* 2007; 185: 249–255.
20. Snijders D, Daniels JMA, de Graaff CS, *et al.* Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. *Am J Respir Crit Care Med* 2010; 181: 975–982.
21. Meijvis SCA, Hardeman H, Remmelts HHF, *et al.* Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; 377: 2023–2030.

22. Fernández-Serrano S, Dorca J, Garcia-Vidal C, *et al.* Effect of corticosteroids on the clinical course of community-acquired pneumonia: a randomized controlled trial. *Crit Care* 2011; 15: R96.
23. Nie W, Zhang Y, Cheng J, *et al.* Corticosteroids in the treatment of community-acquired pneumonia in adults: a meta-analysis. *PLoS One* 2012; 7: e47926.
24. Shafiq M, Mansoor MS, Khan AA, *et al.* Adjuvant steroid therapy in community-acquired pneumonia: a systematic review and meta-analysis. *J Hosp Med* 2013; 8: 68–75.
25. Chen Y, Li K, Pu H, *et al.* Corticosteroids for pneumonia. *Cochrane Database Syst Rev* 2011; 3: CD007720.
26. Merx MW, Weber C. Statins in the intensive care unit. *Curr Opin Crit Care* 2006; 12: 309–314.
27. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999; 282: 2340–2346.
28. Meijvis SCA, van de Garde EMW, Rijkers GT, *et al.* Treatment with anti-inflammatory drugs in community-acquired pneumonia. *J Intern Med* 2012; 272: 25–35.
29. Troeman DPR, Postma DF, van Werkhoven CH, *et al.* The immunomodulatory effects of statins in community-acquired pneumonia: a systematic review. *J Infect* 2013; 67: 93–101.
30. Falagas ME, Makris GC, Matthaiou DK, *et al.* Statins for infection and sepsis: a systematic review of the clinical evidence. *J Antimicrob Chemother* 2008; 61: 774–785.
31. Wunderink RG, Mandell L. Adjunctive therapy in community-acquired pneumonia. *Semin Respir Crit Care Med* 2012; 33: 311–318.
32. Tleyjeh IM, Kashour T, Hakim FA, *et al.* Statins for the prevention and treatment of infections: a systematic review and meta-analysis. *Arch Intern Med* 2009; 169: 1658–1667.
33. Chopra V, Rogers MAM, Buist M, *et al.* Is statin use associated with reduced mortality after pneumonia? A systematic review and meta-analysis. *Am J Med* 2012; 125: 1111–1123.
34. Chalmers JD, Singanayagam A, Murray MP, *et al.* Prior statin use is associated with improved outcomes in community-acquired pneumonia. *Am J Med* 2008; 121: 1002–1007.
35. Majumdar SR, McAlister FA, Eurich DT, *et al.* Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study. *BMJ* 2006; 333: 999.
36. Yende S, Milbrandt EB, Kellum JA, *et al.* Understanding the potential role of statins in pneumonia and sepsis. *Crit Care Med* 2011; 39: 1871–1878.
37. Shrank WH, Polinski JM. Medicare Part D–lessons learned and guidance for health-care reform. *J Gen Intern Med* 2010; 25: 3–4.
38. Corrales-Medina VF, Musher DM, Wells GA, *et al.* Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. *Circulation* 2012; 125: 773–781.
39. Corrales-Medina VF, Musher DM, Shachkina S, *et al.* Acute pneumonia and the cardiovascular system. *Lancet* 2013; 381: 496–505.
40. Maroney SA, Mast AE. Tissue factor pathway inhibitor and bacterial infection. *J Thromb Haemost* 2011; 9: 119–121.
41. Van Den Boogaard FE, Brands X, Schultz MJ, *et al.* Recombinant human tissue factor pathway inhibitor exerts anticoagulant, anti-inflammatory and antimicrobial effects in murine pneumococcal pneumonia. *J Thromb Haemost* 2011; 9: 122–132.
42. Laterre P-F. Beyond antibiotics in severe community-acquired pneumonia: the role and rationale for tissue factor pathway inhibition. *Crit Care* 2008; 12: Suppl. 6, S4.
43. Siempos II, Vardakas KZ, Kopterides P, *et al.* Adjunctive therapies for community-acquired pneumonia: a systematic review. *J Antimicrob Chemother* 2008; 62: 661–668.
44. Laterre P-F, Garber G, Levy H, *et al.* Severe community-acquired pneumonia as a cause of severe sepsis: data from the PROWESS study. *Crit Care Med* 2005; 33: 952–961.
45. Winning J, Reichel J, Eisenhut Y, *et al.* Anti-platelet drugs and outcome in severe infection: clinical impact and underlying mechanisms. *Platelets* 2009; 20: 50–57.
46. Gross AK, Dunn SP, Feola DJ, *et al.* Clopidogrel treatment and the incidence and severity of community acquired pneumonia in a cohort study and meta-analysis of antiplatelet therapy in pneumonia and critical illness. *J Thromb Thrombolysis* 2013; 35: 147–154.
47. Arons MM, Wheeler AP, Bernard GR, *et al.* Effects of ibuprofen on the physiology and survival of hypothermic sepsis. Ibuprofen in Sepsis Study Group. *Crit Care Med* 1999; 27: 699–707.
48. Light RB. Indomethacin and acetylsalicylic acid reduce intrapulmonary shunt in experimental pneumococcal pneumonia. *Am Rev Respir Dis* 1986; 134: 520–525.
49. Voiriot G, Dury S, Parrot A, *et al.* Nonsteroidal antiinflammatory drugs may affect the presentation and course of community-acquired pneumonia. *Chest* 2011; 139: 387–394.
50. Corrales-Medina VF, Musher DM. Immunomodulatory agents in the treatment of community-acquired pneumonia: a systematic review. *J Infect* 2011; 63: 187–199.
51. Bugl S, Wirths S, Müller MR, *et al.* Current insights into neutrophil homeostasis. *Ann N Y Acad Sci* 2012; 1266: 171–178.
52. Cheng AC, Stephens DP, Currie BJ. Granulocyte-colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults. *Cochrane Database Syst Rev* 2007; 2: CD004400.
53. Root RK, Lodato RF, Patrick W, *et al.* Multicenter, double-blind, placebo-controlled study of the use of filgrastim in patients hospitalized with pneumonia and severe sepsis. *Crit Care Med* 2003; 31: 367–373.

54. Wunderink R, Leeper K Jr, Schein R, *et al.* Filgrastim in patients with pneumonia and severe sepsis or septic shock. *Chest* 2001; 119: 523–529.
55. Nelson S, Heyder AM, Stone J, *et al.* A randomized controlled trial of filgrastim for the treatment of hospitalized patients with multilobar pneumonia. *J Infect Dis* 2000; 182: 970–973.
56. Hartung H-P, Mouthon L, Ahmed R, *et al.* Clinical applications of intravenous immunoglobulins (IVIg)–beyond immunodeficiencies and neurology. *Clin Exp Immunol* 2009; 158: Suppl. 1, 23–33.
57. Laupland KB, Kirkpatrick AW, Delaney A. Polyclonal intravenous immunoglobulin for the treatment of severe sepsis and septic shock in critically ill adults: a systematic review and meta-analysis. *Crit Care Med* 2007; 35: 2686–2692.
58. Turgeon AF, Hutton B, Fergusson DA, *et al.* Meta-analysis: intravenous immunoglobulin in critically ill adult patients with sepsis. *Ann Intern Med* 2007; 146: 193–203.
59. Rivers E, Nguyen B, Havstad S, *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345: 1368–1377.
60. Kearon C, Akl EA, Comerota AJ, *et al.* Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141: Suppl. 2, e419S–e494S.
61. Dean NC, Silver MP, Bateman KA, *et al.* Decreased mortality after implementation of a treatment guideline for community-acquired pneumonia. *Am J Med* 2001; 110: 451–457.
62. Cornet AD, Smit EGM, Beishuizen A, *et al.* The role of heparin and allied compounds in the treatment of sepsis. *Thromb Haemost* 2007; 98: 579–586.
63. Tuinman PR, Dixon B, Levi M, *et al.* Nebulized anticoagulants for acute lung injury – a systematic review of preclinical and clinical investigations. *Crit Care* 2012; 16: R70.
64. Rafailidis PI, Matthaiou DK, Varbobitis I, *et al.* Use of ACE inhibitors and risk of community-acquired pneumonia: a review. *Eur J Clin Pharmacol* 2008; 64: 565–573.
65. Van der Maarel-Wierink CD, Vanobbergen JNO, Bronkhorst EM, *et al.* Risk factors for aspiration pneumonia in frail older people: a systematic literature review. *J Am Med Dir Assoc* 2011; 12: 344–354.
66. Shinohara Y, Origasa H. Post-stroke pneumonia prevention by angiotensin-converting enzyme inhibitors: results of a meta-analysis of five studies in Asians. *Adv Ther* 2012; 29: 900–912.
67. Liu C-L, Shau W-Y, Wu C-S, *et al.* Angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers and pneumonia risk among stroke patients. *J Hypertens* 2012; 30: 2223–2229.
68. Okaishi K, Morimoto S, Fukuo K, *et al.* Reduction of risk of pneumonia associated with use of angiotensin I converting enzyme inhibitors in elderly inpatients. *Am J Hypertens* 1999; 12: 778–783.
69. Takahashi T, Morimoto S, Okaishi K, *et al.* Reduction of pneumonia risk by an angiotensin I-converting enzyme inhibitor in elderly Japanese inpatients according to insertion/deletion polymorphism of the angiotensin I-converting enzyme gene. *Am J Hypertens* 2005; 18: 1353–1359.
70. Mortensen EM, Restrepo MI, Anzueto A, *et al.* The impact of prior outpatient ACE inhibitor use on 30-day mortality for patients hospitalized with community-acquired pneumonia. *BMC Pulm Med* 2005; 5: 12.
71. van de Garde EMW, Souverein PC, Hak E, *et al.* Angiotensin-converting enzyme inhibitor use and protection against pneumonia in patients with diabetes. *J Hypertens* 2007; 25: 235–239.
72. Mukamal KJ, Ghimire S, Pandey R, *et al.* Antihypertensive medications and risk of community-acquired pneumonia. *J Hypertens* 2010; 28: 401–405.
73. Mortensen EM, Restrepo MI, Copeland LA, *et al.* Association of hydrophilic *versus* lipophilic angiotensin-converting enzyme inhibitor use on pneumonia-related mortality. *Am J Med Sci* 2008; 336: 462–466.
74. Caldeira D, Alarcão J, Vaz-Carneiro A, *et al.* Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. *BMJ* 2012; 345: e4260.
75. Lipchik RJ. ACP Journal Club. Review: ACE inhibitors reduce risk for pneumonia. *Ann Intern Med* 2012; 157: JC5–2.
76. Mortensen EM, Nakashima B, Cornell J, *et al.* Population-based study of statins, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors on pneumonia-related outcomes. *Clin Infect Dis* 2012; 55: 1466–1473.
77. Ogihara T, Kikuchi K, Matsuoka H, *et al.* The Japanese society of hypertension guidelines for the management of hypertension (JSH 2009). *Hypertens Res* 2009; 32: 3–107.
78. Chang CC, Cheng AC, Chang AB. Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults. *Cochrane Database Syst Rev* 2012; 2: CD006088.
79. Yang M, Yan Y, Yin X, *et al.* Chest physiotherapy for pneumonia in adults. *Cochrane Database Syst Rev* 2013; 2: CD006338.
80. Agrafiotis M. Insufficient evidence to recommend routine adjunctive chest physiotherapy for adults with pneumonia. *Evid Based Med* 2010; 15: 76–77.
81. Pattanshetty RB, Gaude GS. Effect of multimodality chest physiotherapy on the rate of recovery and prevention of complications in patients with mechanical ventilation: a prospective study in medical and surgical intensive care units. *Indian J Med Sci* 2011; 65: 175–185.
82. Castro AAM, Calil SR, Freitas SA, *et al.* Chest physiotherapy effectiveness to reduce hospitalization and mechanical ventilation length of stay, pulmonary infection rate and mortality in ICU patients. *Respir Med* 2013; 107: 68–74.
83. Stiller K. Physiotherapy in intensive care: an updated systematic review. *Chest* 2013; 144: 825–847.

84. Clini E, Ambrosino N. Early physiotherapy in the respiratory intensive care unit. *Respir Med* 2005; 99: 1096–1104.
85. Avendaño M, Güell R. Rehabilitación en pacientes con enfermedades neuromusculares y con deformidades de la caja torácica [Rehabilitation in patients with neuromuscular and chest wall abnormalities]. *Arch Bronconeumol* 2003; 39: 559–565.
86. Lamy O, Van Melle G, Cornuz J, *et al.* Clinical management of immunocompetent hospitalized patients with community-acquired pneumonia. *Eur J Intern Med* 2004; 15: 28–34.
87. Robriquet L, Kipris E, Guery B. Beta-adrenergic modulation of lung fluid balance in acute *P. aeruginosa* pneumonia in rats. *Exp Lung Res* 2011; 37: 453–460.
88. Su X, Robriquet L, Folkesson HG, *et al.* Protective effect of endogenous beta-adrenergic tone on lung fluid balance in acute bacterial pneumonia in mice. *Am J Physiol Lung Cell Mol Physiol* 2006; 290: L769–L776.
89. Miller CC, Hergott CA, Rohan M, *et al.* Inhaled nitric oxide decreases the bacterial load in a rat model of *Pseudomonas aeruginosa* pneumonia. *J Cyst Fibros* 2013; 12: 817–820.
90. Webert KE, Vanderzwan J, Duggan M, *et al.* Effects of inhaled nitric oxide in a rat model of *Pseudomonas aeruginosa* pneumonia. *Crit Care Med* 2000; 28: 2397–2405.
91. Jean D, Maître B, Tankovic J, *et al.* Beneficial effects of nitric oxide inhalation on pulmonary bacterial clearance. *Crit Care Med* 2002; 30: 442–447.
92. Gómez FP, Amado VM, Roca J, *et al.* Effect of nitric oxide inhalation on gas exchange in acute severe pneumonia. *Respir Physiol Neurobiol* 2013; 187: 157–163.

Chapter 17

Inhaled corticosteroids as a cause of CAP

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SUMMARY: Patients suffering from chronic obstructive pulmonary disease (COPD) are more likely to report community-acquired pneumonia than others of a similar age, with approximately 3% of patients per year being affected. COPD patients using inhaled corticosteroids are almost twice as likely to have pneumonia. These pneumonias do not appear to be more severe or confer a higher mortality than similar episodes in non-corticosteroid users. Drugs containing the fluticasone moiety show the strongest association with pneumonia irrespective of the dose used, while data for an association of pneumonia with budesonide is weaker. Pneumonic episodes may represent a failure of prior COPD exacerbations to fully resolve and may be related to a greater microbial load in the lower respiratory tract. To date, no association has been established between pneumonia and inhaled corticosteroid use in asthmatics nor is the oral anti-inflammatory drug roflumilast associated with an excess of pneumonia. More data are needed to allow a proper estimate of the risk/benefit balance of inhaled corticosteroids in COPD.

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Pneumonia, or at least the generic term lower respiratory tract infection, remains a major cause of morbidity globally and is anticipated to remain the fourth most common cause of death worldwide by 2030 [1]. The issues of the diagnostic precision of this term are considered elsewhere in this Monograph. Suffice to say, many diagnoses of pneumonia made in the community are not confirmed radiologically, although this is traditionally seen as the gold standard diagnostic test. However, even here, some caution is needed as more evidence is emerging that alveolar consolidation can be detected with computed tomography when it is not evident on the radiograph. Thus, our ideas about what constitutes clinically important pneumonia are still evolving. These diagnostic concerns became important when determining which clinical characteristics are associated with an increased risk of community-acquired pneumonia (CAP) and in estimating the total number of such events. Similarly, the population studied will determine the frequency with which pneumonia is observed and the severity of the resulting episode. Thus the risk factors for developing pneumonia in someone admitted to an intensive care unit might well differ from an event occurring in a patient managed at home.

Despite these concerns, the profile of risk factors associated with pneumonia is surprisingly similar whether an apparently mild illness or a very severe one results. Principal amongst these are chronic use of tobacco and excess alcohol consumption, as well as the presence of illnesses that modulate

the immune system such as cancer, autoimmune disease, rheumatoid arthritis and diabetes. This list of predisposing factors has not changed significantly over the last 40 years and they have recently been reviewed [2]. However, an important new risk factor, the use of inhaled corticosteroids (ICS), has been identified recently. A PubMed search using the terms "pneumonia" and "inhaled corticosteroids" identified 397 papers up to August 2013, with varying degrees of relevance on this topic. Apart from one Japanese study in 2004 [3], which found no association of pneumonia and ICS in asthmatics, no paper considered whether the use of ICS was associated with an increased risk of pneumonia in chronic obstructive pulmonary disease (COPD) until 2007.

This changed significantly with the publication of the TORCH (Towards a Revolution in COPD Health) study [4], a 3-year, multicentre, international, four-armed, double-blind, placebo-controlled comparison of inhaled steroids, a long-acting β-agonist (LABA), the combination of the two, or placebo. This study was designed to determine whether these drugs reduced mortality in COPD and it did not meet its primary end-point. However, TORCH did identify a significantly greater risk of pneumonia being diagnosed in the COPD patients whose treatment included the ICS fluticasone propionate. Subsequently, multiple studies have reviewed databases or prospectively gathered information about the occurrence of pneumonia in patients treated with inhaled steroids, predominantly those suffering from COPD and these data will be considered in this chapter. Our understanding of the relationship between CAP and ICS use is not yet complete, but important progress has been made.

ICS and pneumonia in COPD

Over the last 15 years, ICS have been shown to reduce the number of exacerbations experienced by COPD patients and improve lung function and quality of life, as well as potentially modifying the rate of decline of forced expiratory volume in 1 s [5–9]. The effects of ICS treatment are generally greater when combined with a LABA, although recent data suggest the use of a long-acting anti-muscarinic drug (LAMA) can be even more effective in exacerbation prevention [10]. Current treatment guidelines recommend ICS/LABA treatment in patients with more severe spirometric impairment and/or a history of recurrent exacerbations. Additionally, combination treatment can be offered to patients with less severe obstructive lung disease whose problems are not controlled by monotherapy with a long-acting bronchodilator [11, 12]. Although COPD has been recognised as an important risk factor in pneumonia for many years, it was not until sufficient patients were studied for a longer period, as in the TORCH study, that the importance of pneumonia in this disease was properly understood.

In brief, the TORCH study randomised 6113 patients to one of four treatment arms: inhaled fluticasone propionate 500 μg daily, inhaled salmeterol (LABA) 50 μg daily, a combination of the two drugs in the same doses in a single inhaler, or a placebo in an identical inhaler [4]. The patients were followed up repeatedly over 3 years or until their death. A range of clinical data was collected at the outset but unfortunately this did not include any blood specimens. Exacerbations of COPD were prospectively defined by the need for antibiotics and/or oral corticosteroids, and data about their occurrence were collected every 3 months throughout the study period.

There was evidence of differential drop out soon after randomisation, with patients receiving placebo therapy being twice as likely to withdraw from the study in the first year as compared with those receiving the combination treatment. This problem has been a consistent finding in treatment studies in COPD [13]. The occurrence of physician-diagnosed pneumonia was either recorded as an adverse event or as a serious adverse event if the patient was hospitalised, while pneumonias treated with antibiotics and oral corticosteroids were also counted as exacerbations and included within that end-point. The study showed that there was a significant decrease in exacerbation numbers in patients who were randomised to receive ICS rather than placebo, but this difference in exacerbation rate was mostly due to a reduction in episodes treated acutely with oral corticosteroids.

When the adverse events were tabulated, it became clear that although pneumonia was substantially less frequent than exacerbation events, it did occur more often in patients who were

receiving the treatments that contained ICS. There was a differential exposure to these drugs, but even when expressed as events per 1000 patient years of treatment, there were significantly more pneumonias in the fluticasone propionate treatment arms (70 *versus* 40 events). Once ICS use was identified as a significant risk factor, attempts were made to place this association on a firmer footing and to determine whether these pneumonias had been radiologically confirmed. In practice, in only 60% of events was there any record that a chest radiograph had been performed and data about these radiographs were not always available [14]. Subsequently the factors associated with a greater risk of having pneumonia in the TORCH study were reviewed and are summarised in figure 1. In general, these were very much the same factors as for pneumonia, with indicators to the presence of worse COPD (worse lung function, dyspnoea and a prior history of exacerbations) increasing the risk of pneumonia being reported. Rather later seasonal variation was shown to be an important risk factor in these patients with increasing risk of exacerbation and pneumonia over the winter period, irrespective of the hemisphere in which the patient lived [15, 16]. However, even when the analysis of the TORCH data was restricted to events that were reported as being radiologically confirmed by the investigator and allowance was made for potential imbalances in risk at baseline, it was clear that there was a significant chance that patients who received fluticasone propionate would develop pneumonia.

As the results of the TORCH study were being analysed, a second study, INSPIRE (Investigating New Standards for Prophylaxis in Reduction of Exacerbations), was approaching its conclusion. This study involved over 1300 COPD patients with a history of prior exacerbations, who were randomised to receive either the combination of fluticasone propionate and salmeterol or the LAMA tiotropium [17]. The primary outcome of this trial was based on the COPD exacerbation rate with the expectation that one treatment would be more effective in preventing exacerbations. The exacerbation rate was similar in each group, although there was a difference in the likelihood of drop-out, which was greater in patients who received LAMA treatment. The INSPIRE data set was smaller than that of the TORCH study, but provided an opportunity to reconfirm the magnitude of risk in a group of patients with more severe COPD. The time to the first pneumonia event in the INSPIRE study is shown in figure 2. Again the problems of pneumonia had not been identified prospectively and so these data also suffered from a lack of routine radiological confirmation. Nonetheless, both the risk factors associated with pneumonia in INSPIRE, and the event rate of approximately 6% per year with fluticasone propionate treatment and 3% of new events per year on LAMA were very similar to values seen in the TORCH study.

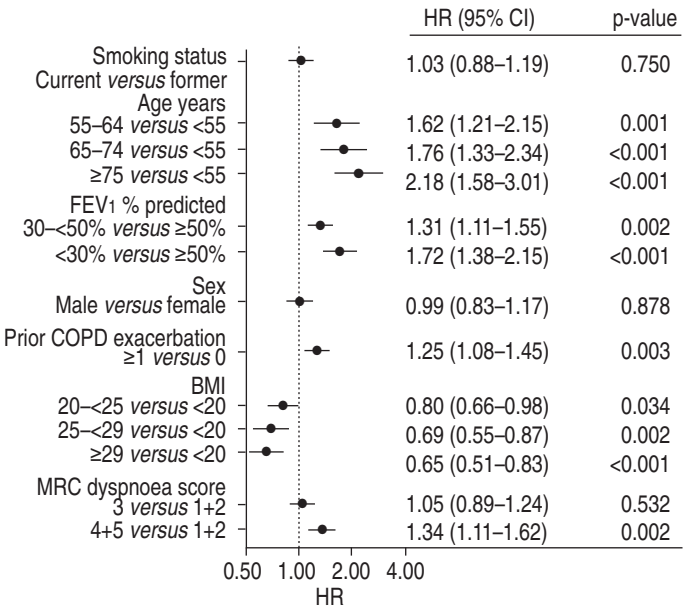

Figure 1. Potential independent risk factors for the occurrence of pneumonia in chronic obstructive pulmonary disease (COPD) patients participating in the TORCH (Towards a Revolution in COPD Health) study. Data are expressed as hazard ratios (HR) with p-values for the significance of difference between the comparisons. FEV1: forced expiratory volume in 1 s; BMI: body mass index; MRC: Medical Research Council. Reproduced from [14].

Interpreting the outcomes of these pneumonic events in clinical trials is not simple. In the TORCH study, ICS treatment successfully reduced the exacerbation rate but did not affect the risk of hospitalisation, although both the ICS/LABA and LABA alone did reduce the risk of hospitalisation. The causes of hospitalisation were not

clear and there was no significant amount of microbiological data available to potentially explain these observations. In the TORCH study, mortality with ICS was numerically but not statistically significantly different from the risk of dying while receiving the placebo. In contrast, the LABA/ICS treatment closely approached statistical significance compared with placebo and was significantly less than that seen with ICS alone. In the 2-year INSPIRE study, LABA/ICS treatment was associated with a statistically significant reduction in mortality compared with LAMA. However, this study was not powered to detect mortality differences and this makes overinterpretation of this finding potentially dangerous. Although a differential rate of pneumonia occurrence was present in these randomised control trials, the event rate was still too low to make definite statements about the impact of corticosteroids on the risk of hospitalisation from pneumonia or on mortality thereafter.

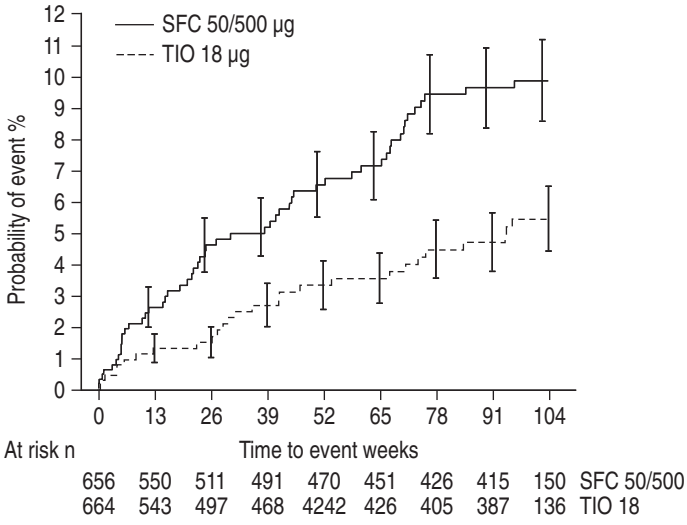

Figure 2. Kaplan–Meier plot showing time to first pneumonia event in patients participating in the INSPIRE (Investigating New Standards for Prophylaxis in Reduction of Exacerbations) trial treated with a salmeterol/fluticasone propionate combination inhaler (SFC) and those receiving inhaled tiotropium (TIO) without inhaled corticosteroids. Numbers at risk are also presented. The probability of event prior to week 104 were 9.9% and 5.5% for SFC and TIO, respectively. Cox hazard ratio 1.94, 95% CI 1.19–3.17; p=0.008. Reproduced from [18] with permission from the publisher.

Given that larger numbers of subjects are required to provide a clearer answer, it was logical to study large administrative databases to try and identify similar associations to those suggested by the randomised control trials. The first group to do this were Canadian investigators who used the Quebec medical data set to confirm that patients prescribed ICS and with physician-diagnosed COPD were more likely to subsequently develop pneumonia than those not receiving this treatment [19]. These data were subsequently challenged by the results of two US data sets, which showed no increase in the risk of pneumonia with ICS treatment, a conclusion that is not in agreement with the consistent pattern seen in randomised controlled trials [20]. One problem here is the familiar issue of confounding by indication. If the patients receiving ICS are also sicker, as the treatment guidelines indicate that they should be, and have worse spirometry then it is difficult to statistically adjust for increased chances of developing pneumonia in a data set where only a moderate number of relevant variables are available. Perhaps more pertinent is the question of whether any events amongst patients receiving ICS are more severe than those occurring in people not receiving ICS. On balance, the evidence here is reassuring. In a prospective observational study from Scotland, UK, patients with spirometrically confirmed COPD and radiologically confirmed pneumonia did not differentiate outcome or length of hospital stay, even if they received ICS as part of their management [21]. Although a recent Canadian study has suggested a greater mortality risk in patients taking high-dose ICS [22], several larger retrospective studies suggested that ICS use was associated with a better outcome in patients hospitalised with pneumonia [23–25]. This raises the possibility that not all pneumonias in ICS-treated patients are the same and carry the same potentially grievous consequences. Indeed, a recent UK database review from 1996–2005 estimated that CAP occurred in 2.24% of COPD patients, especially in those with significant cardiac comorbidity and dementia [26]. This database covers a wider range of patient severity than clinical trials and suggests that pneumonia in primary care populations may be seen less frequently than in patients with more severe disease who are seen in specialist practice.

Dose-related risk

An obvious concern from the outset was whether the risk of pneumonia associated with ICS use could be reduced if the patients took a lower dose of the inhaled steroid. Again, the data are dominated by information about COPD patients and particularly by those who were treated with fluticasone propionate. As part of the US registration programme for fluticasone propionate, two large studies were conducted of LABA/ICS therapy in COPD using half the dose of fluticasone propionate employed in the TORCH and INSPIRE studies and focussing on combination treatment rather than ICS monotherapy [27, 28]. Although this treatment combination was effective in reducing exacerbations, the rate of pneumonic events was similar to that previously reported: 7% on fluticasone propionate and 2% on placebo. More recently, a new once-daily ICS fluticasone furoate has been studied [29]. This drug is chemically related to fluticasone propionate but was considered with a new once-daily LABA, vilanterol. Compared with the LABA and three different doses of fluticasone furoate/LABA, it was clear that more pneumonia occurred with ICS treatment, irrespective of the dose studied. Indeed, at the highest dose of this drug, there was more evidence of fatality associated with pneumonia, although the number of events were small and this difference may have arisen by chance [30].

Does the choice of ICS matter?

Most of the randomised control trial data and much of the information collected in database reviews is applied to fluticasone propionate. There is uncertainty as to whether fluticasone propionate is specifically responsible for the increase in the incidence of pneumonia or whether any change in incidence is a class effect. Although some of the data have been criticised by different experts, there is evidence that not all ICS carry the same risk. Studies with once- and twice-daily mometasone used as a monotherapy in COPD patients did not identify a difference in the reported risk of pneumonia [8]. Much more information is available for the ICS budesonide. A pooled analysis of the risk of pneumonia in predominantly 1-year studies comparing budesonide-containing treatments and placebo has been conducted [31]. There did not appear to be any substantial difference in the way the pneumonia data were collected from the adverse/series event record and, in these trials, there was no observed increase in the rate of pneumonia with budesonide. Again, concerns remain about the lack of radiological verification but the annual rates of pneumonic events, approximately 3% per year for pneumonia reported as an adverse event and 1.5% per year where it was considered a serious adverse event, were entirely comparable with the placebo and β-agonist only rates of the earlier fluticasone propionate studies.

A recent report from a large Scandinavian database has suggested that pneumonia diagnosed in the community is significantly less frequent in patients treated with budesonise than fluticasone propionate, supporting the results of the *post hoc* analysis of the previous studies [32]. These findings are broadly in line with data reviewing the Quebec administrative database where pneumonia was seen less frequently in COPD patients taking budesonide compared with fluticasone propionate [22]. As noted previously, the once-daily inhaled steroid fluticasone furoate is associated with more pneumonia. A particular strength of this study was that the great majority of events were radiologically confirmed. Further analysis of these data is awaited with interest, as it should not only indicate whether there are differences in pneumonias associated with ICS use, but it should provide a body of information that will help inform us about the pattern of radiological abnormality observed in the community in COPD patients.

Mechanistic considerations

Despite much speculation about the mechanisms underlying the excessive pneumonia observed when ICS are used in COPD, the cause of these events, if there is a single cause, remains unclear. Treatment with ICS alone has little effect on airway inflammation in COPD, at least over a few

months of therapy [33, 34], but is associated with an increase in the size of B-cell follicles in pathological specimens obtained from COPD patients undergoing resectional surgery [35]. Since the combination of an ICS and a LABA is associated with less inflammation and a reduced number of airways neutrophils [36], but still carries a similar risk of pneumonia, it seems unlikely that a direct effect on the tissues explains this noticeable difference in incidence. These pathological data suggest that perhaps the main difference lies in the immune stimuli within the airway and recent data have shown that patients who were treated with inhaled steroids have a larger microbiological burden in the lower airways [37]. This raises the possibility that patients taking an ICS, such as fluticasone propionate, have more extensive lower airway colonisation and/or are more likely to develop bacterial infection after a viral illness. Overgrowth of the microbiome has been observed in COPD patients with much milder disease after experimental rhinovirus infection [38]. Experimental data in a mouse model has shown that fluticasone propionate impairs clearance of *Klebsiella pneumoniae* and reduces production of reactive inducible nitric oxide synthase by alveolar macrophages [39].

Data from the INSPIRE study would fit with this suggestion of an altered microbial environment. There was a significant lower likelihood that an exacerbation would be treated with oral corticosteroids if the patient had been randomised to salmeterol/fluticasone propionate combination inhaler rather than tiotropium. Conversely, more exacerbations were treated with antibiotics in the salmeterol/fluticasone propionate combination inhaler group. As part of this trial, diary cards were completed using the questionnaire developed by the group of W. Wedzicha in London, UK, as described in the original study description for the INSPIRE study [40]. The intention was to define episodes of exacerbations, including those that did and did not require specific therapy, but coincidentally has allowed us to look at the recurrent respiratory tract symptoms in individuals who went on to develop pneumonia [18]. For many episodes of pneumonia, little or no preliminary change in symptoms was observed before the diagnosis was made, suggesting a relatively sudden onset of the illness. Events of this type comprise the majority of those seen during tiotropium treatment. A similar number of events appeared in patients receiving LABA/ICS. However, another group of pneumonias were identified as occurring after a period of several weeks of greater than normal symptoms, often following COPD exacerbation. Approximately half of these exacerbations had been treated with antibiotics or corticosteroids. The remaining events met the symptomatic diagnosis of an untreated/unreported event, widely identified in earlier studies of COPD exacerbations and subsequently confirmed as being clinically relevant [41, 42]. These apparently unresolved exacerbations preceding a diagnosis of pneumonia were much more common in patients receiving ICS/LABA treatment than in those who were randomised to tiotropium [18]. There is a need for further study of the fundamental immune mechanisms related to the onset of lower respiratory tract colonisation, which should provide a more robust way of determining whether the apparent difference between different inhaled steroids is a real event or not and whether differences in lower respiratory tract microbiology explain the increase in pneumonia in COPD treated with ICS. Whether differences in chemical properties of individual corticosteroids, such as their degree of lipophilicity, or in pharmacokinetic or pharmacodynamic behaviour within the airway can explain the apparent differences in pneumonia risk remains unclear at this time.

Diseases other than COPD

Whilst most literature about ICS and pneumonia comes from the study of COPD, there are clearly other illnesses where these drugs are used, specifically bronchial asthma. Patients who suffer from asthma are less likely to develop pneumonia as they tend to be younger and nonsmokers; thus, it is not surprising that a large retrospective review of clinical trials conducted with budesonide found no evidence of increased risk of pneumonia [43]. However, this does not exclude some increased risk of pneumonia in asthmatics treated with fluticasone propionate. The GlaxoSmithKline database has been reviewed and apparently no significant signal is present (C. Crim, GlaxoSmithKline, Research Triangle Park, NC, USA; personal communication) but it would be

reassuring to see these findings published in full. This is particularly important given the recent UK database study, which suggested that the pneumonia risk is doubled among patients receiving high-dose ICS [44]. Once again, the issue of confounding by disease severity has become a problem, although the authors of this study tried hard to address this in their data set.

As yet, the role of ICS in less frequent conditions, such as bronchiectasis, has not been examined in relation to the incidence of pneumonia and it is likely that only database investigations will be available to address this issue.

Prevention

All treatment decisions involve an assessment of the treatment risk compared with the potential benefit it offers. Awareness of the use of some ICS-containing treatments in COPD that increase the risk of pneumonia has to be balanced against the established benefits of these treatments. At present, current guidelines still recommend these therapies for the management of patients with severe COPD, although the major international guidelines have alerted readers to this increased pneumonia risk. Specific preventative measures might be beneficial, particularly in dealing with the excess of ICS-related pneumonia due to poorly resolved exacerbations. More aggressive treatment of these episodes, earlier review of the patient to ensure that symptoms having been resolved, or perhaps more wide-spread use of existing immuno-prophylaxis, beginning with influenza and pneumococcal disease, may offer advantages. However, given the relative infrequency of these events and the need to conduct very large studies to establish whether they are helpful, it is likely that we will not be able to properly assess the effectiveness of many potentially valuable interventions.

Pursuing management that optimises the treatment of exacerbations would seem to be the best protection against future problems, and studies on the rate of resolution of these events may serve as a proxy for the future benefit in reducing pneumonia risk. A more radical alternative would be to change the prescribed ICS form to one associated with a lower risk or even to consider other agents, such as the anti-inflammatory drug roflumilast, which has not been associated with an increased risk of pneumonia in a large safety data set [45]. However, this agent has more side-effects than is seen with ICS. Moreover, it is only recommended for patients with frequent exacerbations, severe COPD and chronic bronchitis, although these are individuals who are most likely to report pneumonia.

Conclusion

There is little doubt that ICS based on the fluticasone moiety are associated with an increased risk of clinically diagnosed pneumonia in COPD, although it is not clear if this is also the case in bronchial asthma. Whether these pneumonic events are the same in their clinical presentation and consequences as the more common, more abruptly beginning pneumonias is still unclear, as is the impact of other ICS. Current data suggest that the pneumonias produced are not associated with greater morbidity, longer hospital stays or increased mortality, but developing a systemic illness, even if it pursues a different time course, is likely to impact on the patient's well-being in the long term. There is debate as to whether this impact of inhaled anti-inflammatory treatment is confined to one specific molecule or is a class effect, as yet there is no consensus on the best way of preventing these events.

Whether the use of antibiotic prophylaxis will decrease the incidence of pneumonia is also unknown, although there is evidence that daily antibiotic therapy with a macrolide drug can reduce exacerbations in COPD [46]. Whatever else these insights into ICS and pneumonia have done, they have re-focused our attention on the important role of bacterial colonisation and the mechanisms triggering this in people with chronic airways disease. Future research in these areas is clearly urgently needed if we are to develop more effective ways of managing this problem.

Statement of Interest

P.M.A. Calverley is a member of the board for GSK, Boehringer Ingelheim, Takeda and the UK Department of Health Respiratory Programme. He has received consultancy fees from Novartis and Merck and fees for expert testimony from Forest. He has also received payment for lecture fees or service on speakers' bureaus from Novartis, Pfizer, GSK and AstraZeneca, and fees for travel from Boehringer Ingelheim.

References

1. Lozano R, Naghavi M, Foreman K, *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2095–2128.
2. Sanz Herrero F, Blanquer Olivas J. Microbiology and risk factors for community-acquired pneumonia. *Semin Respir Crit Care Med* 2012; 33: 220–231.
3. To M, To Y, Yamada H, *et al.* Influence of inhaled corticosteroids on community-acquired pneumonia in patients with bronchial asthma. *Intern Med* 2004; 43: 674–678.
4. Calverley PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
5. Burge PS, Calverley PM, Jones PW, *et al.* Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297–1303.
6. Spencer S, Calverley PM, Sherwood Burge P, *et al.* Health status deterioration in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 122–128.
7. Calverley PM, Boonsawat W, Cseke Z, *et al.* Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 22: 912–919.
8. Calverley PM, Rennard S, Nelson HS, *et al.* One-year treatment with mometasone furoate in chronic obstructive pulmonary disease. *Respir Res* 2008; 9: 73.
9. Celli BR, Thomas NE, Anderson JA, *et al.* Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008; 178: 332–338.
10. Vogelmeier C, Hederer B, Glaab T, *et al.* Tiotropium *versus* salmeterol for the prevention of exacerbations of COPD. *N Engl J Med* 2011; 364: 1093–1103.
11. O'Reilly J, Jones MM, Parnham J, *et al.* Management of stable chronic obstructive pulmonary disease in primary and secondary care: summary of updated NICE guidance. *BMJ* 2010; 340: c3134.
12. Vestbo J, Hurd SS, Agusti AG, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013; 187: 347–365.
13. Calverley PM, Spencer S, Willits L, *et al.* Withdrawal from treatment as an outcome in the ISOLDE study of COPD. *Chest* 2003; 124: 1350–1356.
14. Crim C, Calverley PM, Anderson JA, *et al.* Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur Respir J* 2009; 34: 641–647.
15. Jenkins CR, Celli B, Anderson JA, *et al.* Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study. *Eur Respir J* 2012; 39: 38–45.
16. Rabe KF, Fabbri LM, Vogelmeier C, *et al.* Seasonal distribution of COPD exacerbations in the prevention of exacerbations with tiotropium in COPD trial. *Chest* 2013; 143: 711–719.
17. Wedzicha JA, Calverley PM, Seemungal TA, *et al.* The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008; 177: 19–26.
18. Calverley PM, Stockley RA, Seemungal TA, *et al.* Reported pneumonia in patients with COPD: findings from the INSPIRE study. *Chest* 2011; 139: 505–512.
19. Mapel D, Schum M, Yood M, *et al.* Pneumonia among COPD patients using inhaled corticosteroids and long-acting bronchodilators. *Prim Care Respir J* 2010; 19: 109–117.
20. Singanayagam A, Chalmers JD, Akram AR, *et al.* Impact of inhaled corticosteroid use on outcome in COPD patients admitted with pneumonia. *Eur Respir J* 2011; 38: 36–41.
21. Suissa S, Patenaude V, Lapi F, *et al.* Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax* 2013; 68: 1029–1036.
22. Chen D, Restrepo MI, Fine MJ, *et al.* Observational study of inhaled corticosteroids on outcomes for COPD patients with pneumonia. *Am J Respir Crit Care Med* 2011; 184: 312–316.
23. Malo de Molina R, Mortensen EM, Restrepo MI, *et al.* Inhaled corticosteroid use is associated with lower mortality for subjects with COPD and hospitalised with pneumonia. *Eur Respir J* 2010; 36: 751–757.
24. Restrepo MI, Mortensen EM, Anzueto A. Are COPD patients with pneumonia who are taking inhaled corticosteroids at higher risk of dying? *Eur Respir J* 2011; 38: 1–3.
25. Mullerova H, Chigbo C, Hagan GW, *et al.* The natural history of community-acquired pneumonia in COPD patients: a population database analysis. *Respir Med* 2012; 106: 1124–1133.

26. Ferguson GT, Anzueto A, Fei R, *et al.* Effect of fluticasone propionate/salmeterol (250/50 microg) or salmeterol (50 microg) on COPD exacerbations. *Respir Med* 2008; 102: 1099–1108.
27. Anzueto A, Ferguson GT, Feldman G, *et al.* Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes. *COPD* 2009; 6: 320–329.
28. Martinez FJ, Boscia J, Feldman G, *et al.* Fluticasone furoate/vilanterol (100/25; 200/25 mug) improves lung function in COPD: a randomised trial. *Respir Med* 2013; 107: 550–559.
29. Dransfield MT, Bourbeau J, Jones PW, *et al.* Once-daily inhaled fluticasone furoate and vilanterol *versus* vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med* 2013; 1: 210–23.
30. Sin DD, Tashkin D, Zhang X, *et al.* Budesonide and the risk of pneumonia: a meta-analysis of individual patient data. *Lancet* 2009; 374: 712–719.
31. Janson C, Larsson K, Lisspers KH, *et al.* Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting β2 agonist: observational matched cohort study (PATHOS). *BMJ* 2013; 346: f3306.
32. Hattotuwa KL, Gizycki MJ, Ansari TW, *et al.* The effects of inhaled fluticasone on airway inflammation in chronic obstructive pulmonary disease: a double-blind, placebo-controlled biopsy study. *Am J Respir Crit Care Med* 2002; 165: 1592–1596.
33. Bourbeau J, Christodoulopoulos P, Maltais F, *et al.* Effect of salmeterol/fluticasone propionate on airway inflammation in COPD: a randomised controlled trial. *Thorax* 2007; 62: 938–943.
34. Hogg JC, Chu FS, Tan WC, *et al.* Survival after lung volume reduction in chronic obstructive pulmonary disease: insights from small airway pathology. *Am J Respir Crit Care Med* 2007; 176: 454–459.
35. Barnes NC, Qiu YS, Pavord ID, *et al.* Antiinflammatory effects of salmeterol/fluticasone propionate in chronic obstructive lung disease. *Am J Respir Crit Care Med* 2006; 173: 736–743.
36. Garcha DS, Thurston SJ, Patel AR, *et al.* Changes in prevalence and load of airway bacteria using quantitative PCR in stable and exacerbated COPD. *Thorax* 2012; 67: 1075–1080.
37. Molyneaux PL, Mallia P, Cox MJ, *et al.* Outgrowth of the bacterial airway microbiome following rhinovirus exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 188: 1224–1231.
38. Patterson CM, Morrison RL, D'Souza A, *et al.* Inhaled fluticasone propionate impairs pulmonary clearance of *Klebsiella pneumoniae* in mice. *Respir Res* 2012; 13: 40.
39. Seemungal T, Stockley R, Calverley P, *et al.* Investigating new standards for prophylaxis in reduction of exacerbations – the INSPIRE study methodology. *COPD* 2007; 4: 177–183.
40. Ernst P, Gonzalez AV, Brassard P, *et al.* Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia. *Am J Respir Crit Care Med* 2007; 176: 162–166.
41. Donaldson GC, Seemungal TA, Patel IS, *et al.* Longitudinal changes in the nature, severity and frequency of COPD exacerbations. *Eur Respir J* 2003; 22: 931–936.
42. Xu W, Collet JP, Shapiro S, *et al.* Negative impacts of unreported COPD exacerbations on health-related quality of life at 1 year. *Eur Respir J* 2010; 35: 1022–1030.
43. O'Byrne PM, Pedersen S, Carlsson LG, *et al.* Risks of pneumonia in patients with asthma taking inhaled corticosteroids. *Am J Respir Crit Care Med* 2011; 183: 589–595.
44. McKeever T, Harrison TW, Hubbard R, *et al.* Inhaled corticosteroids and the risk of pneumonia in people with asthma: a case control study. *Chest* 2013; 144: 1788–1794.
45. Calverley PM, Rabe KF, Goehring UM, *et al.* Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* 2009; 374: 685–694.
46. Albert RK, Connett J, Bailey WC, *et al.* Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; 365: 689–698.

Chapter 18

Macrolides as anti-inflammatory agents in CAP

Waleed Salih, Philip M. Short and Stuart Schembri

SUMMARY: Macrolides are frequently used antibacterials in the treatment of community acquired pneumonia (CAP). Observational data have suggested that macrolide use in CAP is associated with lower mortality and morbidity. Studies in other chronic respiratory conditions have demonstrated that macrolide antibiotics have anti-inflammatory effects, which extend beyond their antibacterial properties with immunomodulatory effects at multiple stages of the inflammatory cascade, affecting cytokine secretion, inflammatory and structural cells. These may account for some of the benefits seen in observational studies. However the use of macrolides is not without drawbacks; there is growing concern regarding increasing bacterial resistance, tolerability as well as cardiac and aural toxicities. New generation macrolides are being designed to try and overcome these pitfalls by retaining the excellent pharmacokinetics yet providing better safety and tolerability profiles. This review will discuss the rationale behind the use of macrolides in CAP, their anti-inflammatory effects and potential pitfalls.

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Macrolides are a commonly used class of antibiotics. The most frequently used examples are clarithromycin, azithromycin and erythromycin. They were discovered in the early 1950s, with the first macrolide, erythromycin, being isolated from a broth containing the microorganism *Saccharopolyspora erythraea* [1]. Initial clinical use of this macrolide was for the treatment of upper respiratory tract, skin and soft tissue infections caused by susceptible organisms, especially in the penicillin allergic patient [2]. Drug delivery problems, resulting from acid instability, prompted the design of newer macrolides [3]. In the 1970s and 1980s synthetic derivatives of erythromycin, including clarithromycin and azithromycin, were developed. The structural modifications to erythromycin resulted in improved pharmacokinetic profiles and improved tolerance [3, 4].

Macrolides' antimicrobial activity stems from the presence of a macrolide ring as can be seen in figure 1, this is a large 14-, 15-, or 16-membered macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose and desosamine, may be attached [5]. Macrolides have good tissue penetration and antimicrobial activity, mainly against Gram-positive cocci and atypical pathogens.

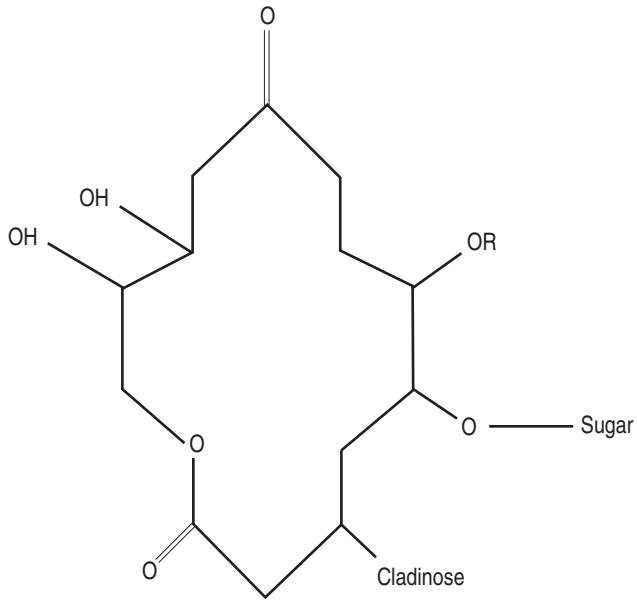

Figure 1. The basic structure of macrolides.

As they have excellent pulmonary penetration, macrolides are frequently used in the treatment of community-acquired pneumonia (CAP) and other respiratory tract infections [5].

The microbiological aetiology of CAP is classically divided into typical and atypical causal organisms. Typical organisms such as; *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* account for approximately 75% of CAP cases [6]. Atypical CAP organisms including *Legionella* species, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* are responsible for the remaining 25% of CAP. In clinical practice, identifying the underlying bacteriology is often elusive, indeed in one study this was only established in 29.6% of hospitalised patients and a mere 5.7% of outpatient CAP episodes [7]. Combination therapy for severe CAP with two antimicrobial agents is recommended in clinical guidelines issued by a number of organisations. The Infectious Diseases Society of America and American Thoracic Society joint guidelines [8] suggest therapy with a β-lactam antibiotic and the addition of either a macrolide or fluoroquinolone antibiotic, whilst the British Thoracic Society recommends initiating a β-lactam/macrolide antibiotic combination [9]. Ensuring cover against atypical organisms is the microbiological rationale behind the recommendation of dual antibiotics.

Macrolides in clinical practice

In several observational studies, macrolide containing antibiotic regimes for the treatment of CAP have been consistently associated with decreased mortality and shorter lengths of hospital stay when compared to antibiotic monotherapy. Such improved outcomes have been reported in pneumonia encompassing the gamut of severity, ranging from mild to life threatening and including ventilator associated pneumonia (VAP) [10–16]. It is worthwhile noting that improvedoutcomes were also noted when macrolide combinations were compared with other therapies with atypical coverage, suggesting that the benefits observed were not simply due to atypical cover [17]. This raises the possibility that macrolide antibiotics have benefits that extend beyond their antibacterial effects. In a randomised study of 200 patients with VAP and sepsis, Giamarellos-Bourboulis *et al.* [18] showed that clarithromycin use resulted in accelerated pneumonia resolution and earlier weaning from mechanical ventilation, although the mortality rate at day 28 was not different.

However, it is difficult to draw firm conclusions from these studies as many were retrospective in nature and often the two groups were so different that making direct comparisons was difficult despite the authors having adjusted for several measured confounding factors. Asadi *et al.* [19] recently reported the results of a meta analysis combining all studies (both observational and randomised trials) studying the effect of macrolide use on mortality in CAP. They included 23 studies and 137 574 patients and showed that macrolides were associated with a 22% reduction in mortality in hospitalised patients with CAP. However, this impressive benefit did not extend to patients included in either prospective studies or those that received guideline concordant therapy [19]. Although there have been several calls for a large prospective randomised study comparing

macrolide containing regimes against non-macrolide combination therapies with similar antimicrobial spectra in the treatment of CAP [19, 20], this is not likely in the near future and for now it is unclear whether the universal use of macrolides is to be associated with improved outcomes. Indeed, a recent Cochrane review, which reviewed randomised controlled studies, did not show a benefit in efficacy or mortality from the empirical use of antimicrobials with atypical cover in the setting of CAP [20].

There is ample evidence that the use of long-term macrolides is associated with improved outcomes in patients with chronic respiratory conditions, such as chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), non CF bronchiectasis, asthma and diffuse panbronchiolitis (DPB) [21]. This is thought to be due to anti-inflammatory effects rather than a pure antimicrobial mechanism. However, unlike their use in chronic diseases, macrolides are only used for a short duration in the setting of CAP. Whether this short-term use is associated with measurable, favourable, clinically significant immunomodulatory effects is in itself controversial.

The aim of this review is to give a comprehensive overview of the potential immunomodulatory effects of macrolide antibiotics with specific reference to their use in CAP.

Immunomodulatory effects of macrolides

Direct immunomodulatory effects

Although macrolides have been used for the past 55 years, mainly for their antibiotic properties, it has become apparent over the last three or four decades that they also have several immunomodulatory effects. Table 1 shows the potential mechanisms through which macrolides achieve their anti-inflammatory effect. These anti-inflammatory properties were first put to clinical use in the treatment of DPB with erythromycin improving the 5-year survival from 63% to 92% [22–24].

The main pro-inflammatory cytokines and chemokines in the setting of infection are tumour necrosis factor (TNF)-α and the interleukins (IL); IL-1β, IL-6 and IL-8. Macrolide antibiotics have been shown to suppress the production of these cytokines in *in vitro* and *in vivo* studies and also in animal models of CAP and other respiratory conditions. Much of the data showing macrolides' immunomodulatory effects derive from studies in healthy participants or patients with chronic respiratory conditions, such as DPB and CF, and it is unclear whether this can be extrapolated to CAP. We will summarise these data first and then discuss the potential application to patients with CAP.

It has been postulated that macrolides achieve attenuated airway cytokine production and secretion *via* the suppression of several transcription factors especially nuclear factor-κB (NF-κB) (NF) and activator protein-1 [25]. Patients with CF have been shown to exhibit larger amounts of neutrophils, TNF-α mRNA and IL-8 in bronchoalveolar lavage fluid (BAL) than non-CF subjects in response to similar levels of infection [26, 27]. The use of azithromycin reduced TNF-α mRNA levels and decreased TNF-α secretion, to approximately the levels of the isogenic non-CF cells [26].

IL-8 is one of the cysteine-X-cysteine chemokines that mobilises, activates and stimulates degranulation of neutrophils. Increased sputum and BAL IL-8 levels have been associated with worse CF and DPB severity [28]. OISHI *et al.* [29] showed that there were significant reductions of neutrophil numbers and IL-8 in BAL of patients with

Table 1. The anti-inflammatory effects of macrolides

Inhibit TNF-α induced mucus secretion
Reduced pro-inflammatory cytokines IL-1β, IL-8 and neutrophils in BAL
Decreased production of TNF-α and IL-6
Decreased TNF-α-induced exotoxin mRNA
Suppress endothelin-1 expression
Induce apoptosis of activated neutrophils
Inhibited NF-κB activation
Suppress TLR expression

TNF: tumour necrosis factor; IL: interleukin; BAL: bronchoalveolar lavage; NF: nuclear factor; TLR: Toll-like receptor.

chronic airway disease when treated with low dose, long-term erythromycin therapy. Erythromycin and clarithromycin also showed a concentration dependent suppression of IL-8 release by eosinophils isolated from atopic subjects [30].

Earlier *ex vivo* studies to demonstrate the immunomodulatory effects of macrolides were carried out in healthy volunteers treated with a 3-day regimen of azithromycin [31]. The study showed a fall in chemokines IL-8 and IL-6 serum concentrations, accompanied by a down regulation of the oxidative burst and an increase in neutrophil apoptosis. The authors concluded that following the administration of the macrolide, azithromycin could enhance endogenous host defence mechanisms by neutrophil degranulation and oxygen burst in response to particulate matter. This complements the direct antibacterial activity of the drug [31].

Other mediators, including IL-1β and leukotriene-B4, are involved in the recruitment and activation of neutrophils in patients with airway infections [32]. These mediators, in addition to IL-8, are present in high levels in the airways of chronic lower respiratory tract infection patients. Studies have demonstrated that treatment with roxithromycin resulted in remarkable clinical improvement, which was associated with decreased cytokine levels [32].

Reports by SAVILL *et al.* [33], in the 1980s, first indicated that neutrophils may be involved in the deterioration of symptoms in patients with chronic inflammatory diseases by producing persistent and excessive oxidants and proteolytic enzymes, which ultimately injure infected or inflamed tissue; therefore, their removal by apoptosis and efferocytosis (clearance of apoptotic neutrophils by macrophages) is a prerequisite of resolution of inflammation. Macrolides have also been shown to inhibit neutrophil migration *via* a number of mechanisms including: decreased adhesion molecules, integrins, and matrix metalloproteinases [34]. INAMURA *et al.* [35] cultured neutrophils in the absence of erythromycin or in the presence of various concentrations of erythromycin for 12 h. They showed that neutrophil apoptosis was significantly enhanced by erythromycin in a dose-dependent manner [35]. Furthermore, findings from AOSHIBA *et al.* [36] suggest that erythromycin shortens neutrophil survival, at least in part, through elevation of intracellular cAMP levels.

Neutrophils and other inflammatory cells need adhesion molecules to migrate into affected airways in response to inflammatory signals [37]. KUSANO *et al.* [38] demonstrated that the expression of these molecules was higher in chronic inflammatory diseases, such as DPB, than in healthy individuals. These levels were decreased following the administration of a macrolide [38].

Although not directly relevant to CAP, endothelin-1 is an important mediator of airway inflammation and is also a potent bronchoconstrictor and vasoconstrictor. These properties give it an important role in asthma-airway hyper responsiveness [39]. TAKIZAWA *et al.* [40] demonstrated that 14-membered macrolides suppressed endothelin-1 expression and release in human bronchoepithelial cells, thus contributing to the attenuation of airway inflammation. Dense neutrophil infiltration in the airways is characteristic of inflammatory airway diseases and increases significantly during airway infection. One major bactericidal mechanism used by neutrophils is the production of reactive oxygen metabolites, together with hydrogen peroxide, hypochlorous acid and hydroxyl radical, during what is referred to as the oxidative burst [41]. However, excessive oxidant generation can also be involved in cell and tissue damage associated with severe inflammatory reaction. Moreover, activated neutrophils in the bronchial lumen are also capable of releasing pro-inflammatory mediators, including IL-8 and TNF-α, which, when combined with toxic oxygen radical species, may subsequently lead to epithelial injury, mucociliary clearance impairment, and mucus hypersecretion [42]. LIN *et al.* [43] showed that erythromycin reduced the intracellular oxidant content of neutrophils, suggesting that the clinically therapeutic effectiveness of erythromycin for these inflammatory airway diseases may be related to a reduction in the intrapulmonary burden of oxidants produced by activated neutrophils [43].

Are these data applicable to patients with CAP?

While there is a clear rationale for the use of macrolides as anti-inflammatory agents in chronic lung conditions, *i.e.* when there is chronic ongoing inflammation, for macrolides to have immunomodulatory properties that affect outcomes in the setting of CAP would require an effect measurable within hours. Furthermore the idea that a beneficial effect may be achieved by dampening the immune response in the setting of sepsis is, in itself, controversial [44]. It has been postulated that while a rampant inflammatory response in the setting of infection originally offered an evolutionary survival advantage, this balance has been tipped following the introduction of antibiotics [45]. Indeed there is data suggesting that anti-inflammatory agents, such as corticosteroids and statins, may offer a survival advantage in certain CAP settings [45]. Figure 2 shows the potential beneficial anti-inflammatory effects of macrolide antibiotics.

Many *in vitro* studies have shown that macrolides suppress cytokine secretion from nasal, bronchial and alveolar cells exposed to CAP-causing pathogens [46]. Such effects have been described when measuring cytokine responses to live pathogens, dead pathogens and bacterial products. VON LONGEVELDE *et al.* [47] demonstrated that whole blood cytokine secretion in response to *Staphylococcus aureus* products was decreased when macrolide antibiotics where used when compared to β-lactams. However, it should be noted that other studies have yielded discordant results [48–51]. Notwithstanding this, the overall data suggest that macrolides do have an immunomodulatory effect that can be measured *in vitro* during acute inflammation.

Macrolides have also been shown to exert additional anti-inflammatory affects by interfering with the structural cells of the respiratory tract. *In vitro* studies have demonstrated that macrolides

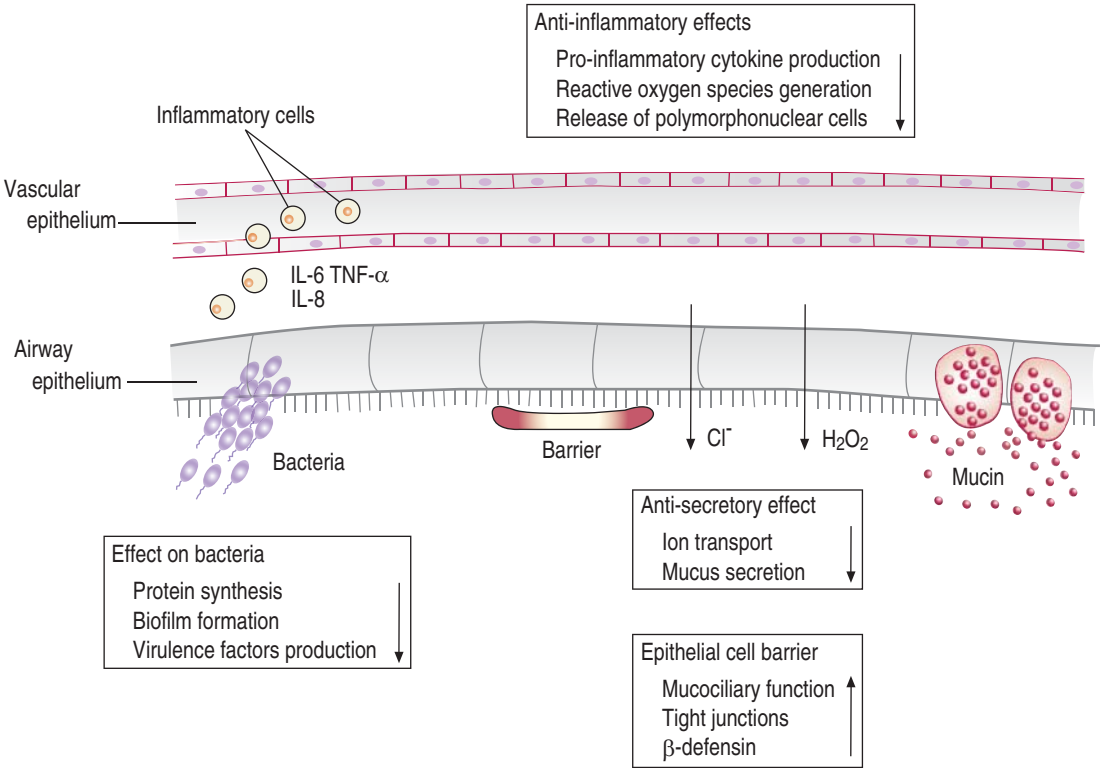

Figure 2. Immunomodulatory effects of macrolides in community-acquired pneumonia. IL: interleukin; TNF: tumour necrosis factor. Arrows indicate direction of flow. Reproduced from [45] with permission from the publisher.

achieve this at a cellular level. URIARTE *et al.* [52] demonstrated that azithromycin and roxithromycin, can inhibit the transendothelial migration of both neutrophils and monocytes when endothelial cells are either infected with *C. pneumoniae* or stimulated with TNF-α. Levels of IL-8 and monocyte chemotactic protein-1 were also decreased in both *C. pneumoniae* infected and TNF-α stimulated human endothelial cells [52].

ABDELAZIZ *et al.* [53] showed that erythromycin may affect neutrophil chemotaxis by modulating the synthesis and/or release of pro-inflammatory mediators, such as IL-8 and soluble intracellular adhesion molecule-1, using cultured human bronchial epithelial cells and adherence assays.

Cytokine studies in animal models of CAP demonstrated that macrolides could attenuate BAL cytokine concentration of mice infected with live bacteria [54–58]. Comparing results from these studies shows that the effect of cytokines is independent on bacterial load, providing further confirmation that macrolides' immunomodulatory effects are independent of their antimicrobial properties. Once again some studies yielded discordant results especially when non-viable bacteria were employed [54–58].

Macrolides have also been shown to have effects on neutrophils in a murine pneumonia model with clarithromycin showing a decrease in neutrophils in BAL of mice infected with *H. influenzae* [59]. Once again there are data that show similar results when macrolide resistant *S. pneumoniae* has been used, suggesting that these immunomodulatory effects are independent of the macrolides' antimicrobial properties. It has been postulated that lower BAL neutrophil counts may be associated with improved outcomes, due to reduced pulmonary collateral damage [60].

DEMARTINI *et al.* [61] compared the effects of clarithromycin and amoxicillin on the plasma levels IL-6, interferon (IFN)-γ and IL-10 in patients with CAP. Inflammatory mediator levels were measured before starting therapy and on the third and seventh days of therapy. They demonstrated that when compared to treatment with amoxicillin, clarithromycin was associated with decreased IL-6 at day 7 and increased IFN-γ and IL-10 at days 3 and 7. Altogether, this resulted in an overall anti-inflammatory effect especially as IL-10 is a major anti-inflammatory cytokine [61].

SPYRIDAKI *et al.* [62] reported the effects of clarithromycin on markers of inflammation in patients participating in a placebo controlled study of clarithromycin in VAP. They obtained blood, both immediately before and on six consecutive days after the administration of the treatment, and showed that patients in the clarithromycin group had a decreased ratio of serum IL-10 to serum TNF-α, along with significantly increased monocyte apoptosis, when compared with the placebo group. Their results suggest that the administration of clarithromycin restored the balance between pro- and anti-inflammatory mediators in patients with sepsis [62].

Although there is promising evidence of a tangible non-antimicrobial benefit from the use of macrolide antibiotics in CAP, one must keep in mind that many of the studies described were small, observational (and, therefore, uncontrolled) or used animal models and at times had discordant results. Although the use of mouse models is a well-established method of studying inflammatory responses, there are few data evaluating how accurately murine models mimic the human inflammatory response. One recent study showed that there was little correlation between murine models and a human response above that of random chance alone [63].

Indirect immunomodulatory effects due to antimicrobial mechanism

Macrolides achieve their antibiotic effect by inhibiting bacterial protein synthesis after reversibly binding to the large 50S bacterial ribosomal subunit. This interaction inhibits RNA-dependent protein synthesis by preventing transpeptidation and translocation reactions [64]. As a

consequence of this they directly inhibit the production of microbial toxins, virulence factors, bacterial adhesins and biofilm, which are pro-inflammatory. *In vitro* studies and animal models have demonstrated the ability of macrolides to attenuate the synthesis of pneumolysin, Panton–Valentine leukocidin and Shiga-like toxins [64–66].

The integrity of the bacterial cell wall remains sound following the use of macrolide antibiotics, unlike with other antibiotic classes that target bacterial cell walls such as the beta lactams. Thus the mode of action of macrolides does not generate damaged disintegrating bacteria which release toxins and cell wall components [65]. Compounds released in this way include pneumococcal toxin, cell wall derived lipopolysaccharides and pneumolysin, which would subsequently activate the complement cascade and initiate an inflammatory response [65]. *In vitro* and *in vivo* models of CAP have demonstrated that such unwanted pro-inflammatory effects are seen following the use of cell wall targeted antibiotic therapies [66–71]. These effects are seen to a lesser degree following macrolide use as its bacteriostatic antimicrobial effects, rather than a sudden bactericidal effect, mean that the bacterial cell wall maintains its structure thus resulting in a dual mechanism of decreased release of bacterial derived inflammatory mediators [65].

New generation macrolides

The prevalence of antibiotic resistance in bacterial pathogens associated with community-acquired respiratory tract infections is increasing [72]. Ketolides are new generation macrolides that are designed to try and overcome this resistance [73]. These agents possess several innovative structural modifications. The ketolides are semi-synthetic derivatives of the 14-membered macrolide erythromycin A, and retain the erythromycin macrolactone ring structure as well as the D-desosamine sugar attached at position 5. The defining characteristic of the ketolides is the removal of the neutral sugar, L-cladinose from the 3 position of the ring and the subsequent oxidation of the 3-hydroxyl to a 3-keto functional group [74]. Hence ketolides exhibit a similar mechanism of action to erythromycin A in that they potently inhibit protein synthesis by interacting close to the peptidyl transferase site of the bacterial 50S ribosomal subunit but with a higher affinity than the available macrolides. They have excellent activity against drug-resistant *S. pneumoniae*, including macrolide-resistant *mefA* and *ermB* strains [75, 76].

Telithromycin (HMR 3647) was the first ketolide to undergo clinical assessment. Telithromycin binds to similar sites targeted by macrolides, domains V and II of the 23S rRNA, but with at least a tenfold higher affinity relative to erythromycin. This is accounted for, at least in part, by stronger binding at domain II [74, 77]. Telithromycin displays excellent pharmacokinetics allowing one daily dose administration and extensive tissue distribution relative to serum. The potent antimicrobial activity of telithromycin also extends to atypical and intracellular pathogens, such as *M. pneumoniae, C. pneumoniae*, and *Legionella* species [78]. It must be noted that the US Food and Drug Administration have mandated a black box warning on telithromycin stating that it is contraindicated in patients with myasthenia gravis and has been associated with severe hepatotoxicity [79].

The potential of achieving anti-inflammatory effects by using macrolide derived drugs that do not have anti-microbial properties is particularly enticing especially in the setting of chronic respiratory conditions where long-term treatment is being considered. Recent developments include (8R,9S)-8,9-dihydro-6,9-epoxy-8,9-anhydropseudoerythromycin (EM900), which is a new erythromycin derivative that has been shown to suppress the induction of inflammatory cytokines in cells derived from human airway epithelia [80].

The pitfalls

Prior to considering a more widespread use of macrolide antibiotics one must also consider the potential pitfalls, these are summarised in table 2.

Table 2. The main pitfalls of macrolide use

Tolerability
Antimicrobial resistance
Cardiovascular toxicity
Hearing loss
Drug interactions

Tolerability

Macrolides are often poorly tolerated due to gastrointestinal side-effects due to the endogenous release of motilin. Such adverse effects may be seen in up to 20% of patients after the use of earlier macrolides, such as erythromycin. Similar, though milder, effects are seen in less than 5% of individuals treated with more recently developed macrolide derivatives such as clarithromycin or azithromycin [81].

Antimicrobial resistance

Antimicrobial resistance presents an ever increasing global public health threat that involves all major microbial pathogens and antibiotic classes [82]. The number of resistant organisms, the geographic locations affected by drug resistance, and the breadth of resistance in single organisms is unprecedented and mounting [82]. Fuelled by increasing antimicrobial use, the frequency of resistance is escalating in many different bacteria, especially in developing countries. The problem of resistance can be seen simplistically as an equation with two main components: the antibiotic or antimicrobial drug, which inhibits susceptible organisms and selects the resistant ones; and the genetic resistance determinant in microorganisms selected by the antimicrobial drug. Many organisms are now either resistant to macrolides or are rapidly developing resistance, MALHOTRA-KUMAR *et al.* [83] demonstrated this in their study investigating the effects of azithromycin and clarithromycin on the resistance in the oral *S. pneumoniae* flora of 204 healthy volunteers. They showed that after 180 days of treatment, both macrolides significantly increased the proportion of macrolide-resistant streptococci compared with the placebo at all points studied, peaking at day 8 in the clarithromycin group with a mean increase of 50% and at day 4 in the azithromycin group with a mean increase of 53·4% [83].

Resistance can be explained by three main mechanisms. As explained earlier, macrolides work by binding to the major 50S subunit of the bacterial ribosome. Resistance may occur due to target-site alteration, alteration in antibiotic transport and/or modification of the antibiotic. The target site may be methylated preventing the macrolide from binding to the ribosome. This process is mediated by the *ermB* gene and results to a high level of macrolide resistance. In 2002 FARRELL *et al.* [84] reported on the PROTEKT study, a global study on the antibacterial susceptibility of bacterial pathogens associated with lower respiratory tract infections. The authors reported that the most commonest cause of macrolide resistance was mediated *via* the *ermB* gene. They also proposed a second mechanism encoded by the *mefA* gene. This involves an active drug efflux mechanism, which is determined by the presence of the membrane-bound efflux protein encoded by the gene. A third mechanism involves an alteration to the binding site of the macrolides [84]. The mutation is in the 23S rRNA and accounts for a small minority of cases in the PROTEKT study [72]. Furthermore, resistance to macrolides is often associated with resistance to tetracyclines and/or aminoglycosides *via* shared targets [85].

Cardiovascular toxicity

The other major concern of macrolide use is their potential cardiac toxicity. Traditionally this was thought to be due to effects on QT prolongation while taking the agents. Such concerns were first raised on a large scale following a study on the effects of erythromycin and sudden cardiac death. The authors studied 1 249 943 person-years and 1476 cases of confirmed sudden death from cardiac causes. Their results showed that patients who used both erythromycin and CYP3A inhibitors had a five times increased risk of sudden death from cardiac causes when compared to those who did not use this combination [86]. Similar large observational studies on azithromycin's effect on sudden cardiac death have yielded discordant results, although mortality rates, age and presence of cardiovascular disease varied significantly between the two populations studied [87, 88].

More recently, concerns have been raised about a potential for clarithromycin to increase ischaemic cardiac events. The association between clarithromycin use and increased ischaemic cardiovascular mortality was first reported in the CLARICOR study and more recently in an analysis of two large prospective datasets [89, 90]. The CLARICOR study was a large randomized, placebo controlled multicentre trial that recruited 4373 participants with stable coronary heart disease who received either 2 weeks of clarithromycin or placebo. Clarithromycin was used to treat presumptive subclinical *Chlamydophila* infection in view of a prevailing hypothesis that *Chlamydophila* infection caused cardiovascular events. Unexpectedly, all-cause mortality was significantly higher in the clarithromycin group (hazards ratio (HR) 1.27 (95% CI 1.03–1.54) p=0.03), as a result of significantly higher cardiovascular mortality (HR 1.45 (95% CI 1.09–1.92) p=0.01). Importantly unlike the effect of macrolides on QT interval associated mortality, these excess cardiac events were noted beyond the time of prescription extending to up to 3 years following clarithromycin administration. A similar increase in cardiovascular events, although not of cardiovascular mortality was recently reported in an observational study of clarithromycin use following hospitalisation for either CAP or acute exacerbations of COPD [90].

Hearing loss

ALBERT *et al.* [91] recently reported a study of 1142 people with severe COPD randomised to either azithromycin or placebo for 1 year. Although azithromycin was associated with fewer COPD exacerbations, the authors noted an absolute 5% excess in hearing loss in the azithromycin treated arm. Most of the hearing loss was reversible with discontinuation of azithromycin, but in some cases was permanent. These rates of ototoxicity exceed the previously believed risks of azithromycin induced hearing loss, which was limited to about 25 case reports, almost all of which reported reversible hearing loss. Interestingly the study by ALBERT *et al.* [91] did not report increased cardiovascular events.

Drug interactions

Macrolide antibiotics are been well recognised to interact with many drugs. The mechanism has been shown to involve inhibiting the CYP3A mediated catalytic activity [92]. Macrolides, therefore, interfere with substrates of CYP3A. These include benzodiazepines, neuroleptics, 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors and warfarin. For example, GREENBLATT *et al* [93] showed that clarithromycin and erythromycin are potent inhibitors of the benzodiazepine triazolam. This resulted in increased peak plasma concentrations, prolonged elimination half-life, and decreased markedly the apparent oral clearance [93]. In a clinical pharmacokinetic study, erythromycin twice daily for 2 days resulted in a sixfold increase of the area under the curve of serum simvastatin [94].

There are reports describing an increase in the hypoprothrombinaemic effect of warfarin following the administration of erythromycin [95]. Interactions of macrolides with theophylline are also well documented. In most studies, erythromycin and clarithromycin decreased theophylline clearance by 20–25% after 7 days of concomitant administration [95].

Conclusions

It is already routine practice to prescribe macrolides for their anti-inflammatory effects in chronic respiratory conditions such as DPB, bronchiectasis and COPD. In this chapter we have described evidence on how the use of macrolides in CAP may have beneficial effects, independent of the antimicrobial properties, thereby providing biological support for the observational studies that show macrolide use to be associated with lower mortality and morbidity in CAP. Macrolides have immunomodulatory effects at multiple stages of the inflammatory cascade, affecting cytokine secretion, inflammatory and structural cells. However, the use of macrolides is not without its pitfalls and there is growing concern regarding bacterial resistance and possible cardiac toxicity. A

large multicentre, randomised controlled trial comparing the use of macrolide and β-lactam combination therapy against β-lactam alone in the setting of CAP is long overdue in order to establish a concrete evidence base.

Statement of Interest

None declared.

References

1. Woodward RB, Logusch E, Nambiar KP, *et al.* Asymmetric total synthesis of erythromcin. 1. Synthesis of an erythronolide a seco acid derivative *via* asymmetric induction. *J Am Chem Soc* 1981; 103: 3210–3213.
2. Waddington WS, Maple FM, Kirby WM. Treatment of bacterial pneumonia with erythromycin. *AMA Arch Intern Med* 1954; 93: 556–560.
3. Gaynor M, Mankin AS. Macrolide antibiotics: binding site, mechanism of action, resistance. *Curr Top Med Chem* 2003; 3: 949–961.
4. Leclercq R, Courvalin P. Resistance to macrolides and related antibiotics in *Streptococcus pneumoniae. Antimicrob Agents Chemother* 2002; 46: 2727–2734.
5. Zuckerman JM. Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. *Infect Dis Clin North Am* 2004; 18: 621–649.
6. Ruiz M, Ewig S, Marcos MA, *et al.* Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. *Am J Respir Crit Care Med* 1999; 160: 397–405.
7. Fine MJ, Stone RA, Singer DE, *et al.* Processes and outcomes of care for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team (PORT) cohort study. *Arch Intern Med* 1999; 159: 970–980.
8. Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44: Suppl. 2, S27–S72.
9. Lim WS, Baudouin SV, George RC, *et al.* BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; 64: Suppl. 3, iii1–iii55.
10. Stahl JE, Barza M, DesJardin J, *et al.* Effect of macrolides as part of initial empiric therapy on length of stay in patients hospitalized with community-acquired pneumonia. *Arch Intern Med* 1999; 159: 2576–2580.
11. Martinez JA, Horcajada JP, Almela M, *et al.* Addition of a macrolide to a β-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis* 2003; 36: 389–395.
12. Brown RB, Iannini P, Gross P, *et al.* Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. *Chest* 2003; 123: 1503–1511.
13. Sligl WI, Asadi L, Eurich DT, *et al.* Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. *Crit Care Med* 2013 [In press DOI: 10.1097/CCM.0b013e3182a66b9b].
14. Restrepo MI, Mortensen EM, Waterer GW, *et al.* Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. *Eur Respir J* 2009; 33: 153–159.
15. Martin-Loeches I, Lisboa T, Rodriguez A, *et al.* Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intensive Care Med* 2010; 36: 612–620.
16. Rodríguez A, Mendia A, Sirvent JM, *et al.* Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. *Crit Care Med* 2007; 35: 1493–1498.
17. Lodise TP, Kwa A, Cosler L, *et al.* Comparison of β-lactam and macrolide combination therapy *versus* fluoroquinolone monotherapy in hospitalized Veterans Affairs patients with community-acquired pneumonia. *Antimicrob Agents Chemother* 2007; 51: 3977–3982.
18. Giamarellos-Bourboulis EJ, Pechère JC, Routsi C, *et al.* Effect of clarithromycin in patients with sepsis and ventilator-associated pneumonia. *Clin Infect Dis* 2008; 46: 1157–1164.
19. Asadi L, Sligl WI, Eurich DT, *et al.* Macrolide-based regimens and mortality in hospitalized patients with community-acquired pneumonia: a systematic review and meta-analysis. *Clin Infect Dis* 2012; 55: 371–380.
20. Eliakim-Raz N, Robenshtok E, Shefet D, *et al.* Empiric antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults. *Cochrane Database Syst Rev* 2012; 9: CD004418.pub4.
21. Amsden GW. Anti-inflammatory effects of macrolides – an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? *J Antimicrob Chemother* 2005; 55: 10–21.
22. Kudoh S. Erythromycin treatment in diffuse panbronchiolitis. *Curr Opin Pulm Med* 1998; 4: 116–121.
23. Kudoh S, Azuma A, Yamamoto M, *et al.* Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. *Am J Respir Crit Care Med* 1998; 157: 1829–1832.
24. Yamamoto M, Kondo A, Tamura M, *et al.* [Long-term therapeutic effects of erythromycin and newquinolone antibacterial agents on diffuse panbronchiolitis]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1990; 28: 1305–1313.

25. Aoki Y, Kao PN. Erythromycin inhibits transcriptional activation of NF-κB, but not NFAT, through calcineurin-independent signaling in T cells. *Antimicrob Agents Chemother* 1999; 43: 2678–2684.
26. Cigana C, Assael BM, Melotti P. Azithromycin selectively reduces tumor necrosis factor alpha levels in cystic fibrosis airway epithelial cells. *Antimicrob Agents Chemother* 2007; 51: 975–981.
27. Tsai WC, Rodriguez ML, Young KS, *et al.* Azithromycin blocks neutrophil recruitment in Pseudomonas endobronchial infection. *Am J Respir Crit Care Med* 2004; 170: 1331–1339.
28. Sakito O, Kadota J, Kohno S, *et al.* Interleukin 1β, tumor necrosis factor α, and interleukin 8 in bronchoalveolar lavage fluid of patients with diffuse panbronchiolitis: a potential mechanism of macrolide therapy. *Respiration* 1996; 63: 42–48.
29. Oishi K, Sonoda F, Kobayashi S, *et al.* Role of interleukin-8 (IL-8) and an inhibitory effect of erythromycin on IL-8 release in the airways of patients with chronic airway diseases. *Infect Immun* 1994; 62: 4145–4152.
30. Kohyama T, Takizawa H, Kawasaki S, *et al.* Fourteen-member macrolides inhibit interleukin-8 release by human eosinophils from atopic donors. *Antimicrob Agents Chemother* 1999; 43: 907–911.
31. Culić O, Eraković V, Cepelak I, *et al.* Azithromycin modulates neutrophil function and circulating inflammatory mediators in healthy human subjects. *Eur J Pharmacol* 2002; 450: 277–289.
32. Nakamura H, Fujishima S, Inoue T, *et al.* Clinical and immunoregulatory effects of roxithromycin therapy for chronic respiratory tract infection. *Eur Respir J* 1999; 13: 1371–1379.
33. Savill JS, Wyllie AH, Henson JE, *et al.* Macrophage phagocytosis of aging neutrophils in inflammation. Programmed cell death in the neutrophil leads to its recognition by macrophages. *J Clin Invest* 1989; 83: 865–875.
34. Kanai K, Asano K, Hisamitsu T, *et al.* Suppression of matrix metalloproteinase production from nasal fibroblasts by macrolide antibiotics *in vitro*. *Eur Respir J* 2004; 23: 671–678.
35. Inamura K, Ohta N, Fukase S, *et al.* The effects of erythromycin on human peripheral neutrophil apoptosis. *Rhinology* 2000; 38: 124–129.
36. Aoshiba K, Nagai A, Konno K. Erythromycin shortens neutrophil survival by accelerating apoptosis. *Antimicrob Agents Chemother* 1995; 39: 872–877.
37. Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. *Clin Microbiol Rev* 2010; 23: 590–615.
38. Kusano S, Kadota J, Kohno S, *et al.* Effect of roxithromycin on peripheral neutrophil adhesion molecules in patients with chronic lower respiratory tract disease. *Respiration* 1995; 62: 217–222.
39. Finsnes F, Skjønsberg OH, Tønnessen T, *et al.* Endothelin production and effects of endothelin antagonism during experimental airway inflammation. *Am J Respir Crit Care Med* 1997; 155: 1404–1412.
40. Takizawa H, Desaki M, Ohtoshi T, *et al.* Erythromycin and clarithromycin attenuate cytokine-induced endothelin-1 expression in human bronchial epithelial cells. *Eur Respir J* 1998; 12: 57–63.
41. Perry DK, Hand WL, Edmondson DE, *et al.* Role of phospholipase D-derived diradylglycerol in the activation of the human neutrophil respiratory burst oxidase. Inhibition by phosphatidic acid phosphohydrolase inhibitors. *J Immunol* 1992; 149: 2749–2758.
42. Sibille Y, Reynolds HY. Macrophages and polymorphonuclear neutrophils in lung defense and injury. *Am Rev Respir Dis* 1990; 141: 471–501.
43. Lin CC, Liaw SF, Wu KM, *et al.* Effect of erythromycin on bronchial hyperreactivity and inflammation in ovalbumin-sensitized brown Norway rats. *Respir Physiol Neurobiol* 2008; 161: 267–272.
44. Weitzman S, Berger S. Clinical trial design in studies of corticosteroids for bacterial infections. *Ann Intern Med* 1974; 81: 36–42.
45. Meijvis SC, van de Garde EM, Rijkers GT, *et al.* Treatment with anti-inflammatory drugs in community-acquired pneumonia. *J Intern Med* 2012; 272: 25–35.
46. Morikawa K, Zhang J, Nonaka M, *et al.* Modulatory effect of macrolide antibiotics on the Th1- and Th2-type cytokine production. *Int J Antimicrob Agents* 2002; 19: 53–59.
47. Van Langevelde P, van Dissel JT, Ravensbergen E, *et al.* Antibiotic-induced release of lipoteichoic acid and peptidoglycan from *Staphylococcus aureus*: quantitative measurements and biological reactivities. *Antimicrob Agents Chemother* 1998; 42: 3073–3078.
48. Lagrou K, Peetermans WE, Jorissen M, *et al.* Subinhibitory concentrations of erythromycin reduce pneumococcal adherence to respiratory epithelial cells *in vitro*. *J Antimicrob Chemother* 2000; 46: 717–723.
49. Kazachkov MY, Hu PC, Carson JL, *et al.* Release of cytokines by human nasal epithelial cells and peripheral blood mononuclear cells infected with *Mycoplasma pneumoniae*. *Exp Biol Med (Maywood)* 2002; 227: 330–335.
50. Koch CC, Esteban DJ, Chin AC, *et al.* Apoptosis, oxidative metabolism and interleukin-8 production in human neutrophils exposed to azithromycin: effects of *Streptococcus pneumoniae*. *J Antimicrob Chemother* 2000; 46: 19–26.
51. Chmura K, Bai X, Nakamura M, *et al.* Induction of IL-8 by *Mycoplasma pneumoniae* membrane in BEAS-2B cells. *Am J Physiol Lung Cell Mol Physiol* 2008; 295: L220–L30.
52. Uriarte SM, Molestina RE, Miller RD, *et al.* Effect of macrolide antibiotics on human endothelial cells activated by *Chlamydia pneumoniae* infection and tumor necrosis factor-α. *J Infect Dis* 2002; 185: 1631–1636.
53. Abdelaziz MM, Devalia JL, Khair OA, *et al.* The effect of conditioned medium from cultured human bronchial epithelial cells on eosinophil and neutrophil chemotaxis and adherence *in vitro*. *Am J Respir Cell Mol Biol* 1995; 13: 728–737.

54. Rios AM, Fonseca-Aten M, Mejías A, *et al.* Microbiologic and immunologic evaluation of a single high dose of azithromycin for treatment of experimental *Mycoplasma pneumoniae* pneumonia. *Antimicrob Agents Chemother* 2005; 49: 3970–3973.
55. Rios AM, Mejias A, Chavez-Bueno S, *et al.* Impact of cethromycin (ABT-773) therapy on microbiological, histologic, immunologic, and respiratory indices in a murine model of *Mycoplasma pneumoniae* lower respiratory infection. *Antimicrob Agents Chemother* 2004; 48: 2897–2904.
56. Hardy RD, Rios AM, Chavez-Bueno S, *et al.* Antimicrobial and immunologic activities of clarithromycin in a murine model of *Mycoplasma pneumoniae*-induced pneumonia. *Antimicrob Agents Chemother* 2003; 47: 1614–1620.
57. Duong M, Simard M, Bergeron Y, *et al.* Kinetic study of the inflammatory response in *Streptococcus pneumoniae* experimental pneumonia treated with the ketolide HMR 3004. *Antimicrob Agents Chemother* 2001; 45: 252–262.
58. Tagliabue C, Salvatore CM, Techasaensiri C, *et al.* The impact of steroids given with macrolide therapy on experimental *Mycoplasma pneumoniae* respiratory infection. *J Infect Dis* 2008; 198: 1180–1188.
59. Nakamura S, Yanagihara K, Araki N, *et al.* Efficacy of clarithromycin against experimentally induced pneumonia caused by clarithromycin-resistant *Haemophilus influenzae* in mice. *Antimicrob Agents Chemother* 2010; 54: 757–762.
60. Yasuda Y, Kasahara K, Mizuno F, *et al.* Roxithromycin favorably modifies the initial phase of resistance against infection with macrolide-resistant *Streptococcus pneumoniae* in a murine pneumonia model. *Antimicrob Agents Chemother* 2007; 51: 1741–1752.
61. Demartini G, Esposti D, Marthyn P, *et al.* Effect of multiple doses of clarithromycin and amoxicillin on IL-6, IFNγ and IL-10 plasma levels in patients with community acquired pneumonia. *J Chemother* 2004; 16: 82–85.
62. Spyridaki A, Raftogiannis M, Antonopoulou A, *et al.* Effect of clarithromycin in inflammatory markers of patients with ventilator-associated pneumonia and sepsis cause by Gram-negative bacteria: results from a randomized clinical study. *Antimicrob Agents Chemother* 2012; 56: 3819–3825.
63. Seok J, Warren HS, Cuenca AG, *et al.* Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc Natl Acad Sci USA* 2013; 110: 3507–3512.
64. Anderson R, Steel HC, Cockeran R, *et al.* Comparison of the effects of macrolides, amoxicillin, ceftriaxone, doxycycline, tobramycin and fluoroquinolones, on the production of pneumolysin by *Streptococcus pneumoniae in vitro. J Antimicrob Chemother* 2007; 60: 1155–1158.
65. Steel HC, Theron AJ, Cockeran R, *et al.* Pathogen- and host-directed anti-inflammatory activities of macrolide antibiotics. *Mediators Inflamm* 2012; 2012: 584262.
66. Kimmitt PT, Harwood CR, Barer MR. Induction of type 2 Shiga toxin synthesis in *Escherichia coli* O157 by 4-quinolones. *Lancet* 1999; 353: 1588–1589.
67. Wong CS, Jelacic S, Habeeb RL, *et al.* The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. *N Engl J Med* 2000; 342: 1930–1936.
68. Stevens DL, Ma Y, Salmi DB, *et al.* Impact of antibiotics on expression of virulence-associated exotoxin genes in methicillin-sensitive and methicillin-resistant *Staphylococcus aureus. J Infect Dis* 2007; 195: 202–211.
69. Dumitrescu O, Badiou C, Bes M, *et al.* Effect of antibiotics, alone and in combination, on Panton-Valentine leukocidin production by a *Staphylococcus aureus* reference strain. *Clin Microbiol Infect* 2008; 14: 384–388.
70. Serna At., Boedeker EC. Pathogenesis and treatment of Shiga toxin-producing *Escherichia coli* infections. *Curr Opin Gastroenterol* 2008; 24: 38–47.
71. McGannon CM, Fuller CA, Weiss AA. Different classes of antibiotics differentially influence shiga toxin production. *Antimicrob Agents Chemother* 2010; 54: 3790–3798.
72. Karchmer AW. Increased antibiotic resistance in respiratory tract pathogens: PROTEKT US – an update. *Clin Infect Dis* 2004; 39: Suppl. 3, S142–S150.
73. Zhanel GG, Hoban DJ. Ketolides in the treatment of respiratory infections. *Expert Opin Pharmacother* 2002; 3: 277–297.
74. Hansen LH, Mauvais P, Douthwaite S. The macrolide-ketolide antibiotic binding site is formed by structures in domains II and V of 23S ribosomal RNA. *Mol Microbiol* 1999; 31: 623–631.
75. Agouridas C, Denis A, Auger JM, *et al.* Synthesis and antibacterial activity of ketolides (6-O-methyl-3-oxoerythromycin derivatives): a new class of antibacterials highly potent against macrolide-resistant and -susceptible respiratory pathogens. *J Med Chem* 1988; 41: 4080–4100.
76. Descheemaeker P, Chapelle S, Lammens C, *et al.* Macrolide resistance and erythromycin resistance determinants among Belgian *Streptococcus pyogenes* and *Streptococcus pneumoniae* isolates. *J Antimicrob Chemother.* 2000; 45: 167–173.
77. Xiong L, Shah S, Mauvais P, *et al.* A ketolide resistance mutation in domain II of 23S rRNA reveals the proximity of hairpin 35 to the peptidyl transferase centre. *Mol Microbiol* 1999; 31: 633–639.
78. Yamaguchi T, Hirakata Y, Izumikawa K, *et al. In vitro* activity of telithromycin (HMR3647), a new ketolide, against clinical isolates of *Mycoplasma pneumoniae* in Japan. *Antimicrob Agents Chemother* 2000; 44: 1381–1382.
79. US Food and Drug Federation. Ketek (telithromyin). www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm152681.htm Date last accessed: October 2013. Date last updated: 2007.

80. Otsu K, Ishinaga H, Suzuki S, *et al.* Effects of a novel nonantibiotic macrolide, EM900, on cytokine and mucin gene expression in a human airway epithelial cell line. *Pharmacology* 2011; 88: 327–332.
81. Periti P, Mazzei T, Mini E, *et al.* Adverse effects of macrolide antibacterials. *Drug Saf* 1993; 9: 346–364.
82. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. *Nat Med* 2004; 10: S122–S129.
83. Malhotra-Kumar S, Lammens C, Coenen S, *et al.* Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet* 2007; 369: 482–490.
84. Farrell DJ, Morrissey I, Bakker S, *et al.* Molecular characterization of macrolide resistance mechanisms among *Streptococcus pneumoniae* and *Streptococcus pyogenes* isolated from the PROTEKT 1999–2000 study. *J Antimicrob Chemother* 2002; 50: Suppl. S1, 39–47.
85. Doern GV, Brown SD. Antimicrobial susceptibility among community-acquired respiratory tract pathogens in the USA: data from PROTEKT US 2000-01. *J Infect* 2004; 48: 56–65.
86. Ray WA, Murray KT, Meredith S, *et al.* Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 2004; 351: 1089–1096.
87. Svanström H, Pasternak B, Hviid A. Cardiovascular risks with azithromycin. *N Engl J Med* 2013; 369: 580–581.
88. Ray WA, Murray KT, Hall K, *et al.* Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012; 366: 1881–1890.
89. Jespersen CM, Als-Nielsen B, Damgaard M, *et al.* Randomised placebo controlled multicentre trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial. *BMJ* 2006; 332: 22–27.
90. Schembri S, Williamson PA, Short PM, *et al.* Cardiovascular events after clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies. *BMJ* 2013; 346: f1235.
91. Albert RK, Connett J, Woodruff PG. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012; 367: 773–774.
92. Pessayre D, Larrey D, Funck-Brentano C, *et al.* Drug interactions and hepatitis produced by some macrolide antibiotics. *J Antimicrob Chemother* 1985; 16: Suppl. A, 181–194.
93. Greenblatt DJ, von Moltke LL, Harmatz JS, *et al.* Inhibition of triazolam clearance by macrolide antimicrobial agents: *in vitro* correlates and dynamic consequences. *Clin Pharmacol Ther* 1998; 64: 278–285.
94. Kantola T, Kivistö KT, Neuvonen PJ. Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998; 64: 177–182.
95. Von Rosensteil NA, Adam D. Macrolide antibacterials. Drug interactions of clinical significance. *Drug Saf* 1995; 13: 105–122.

Chapter 19

Cardiovascular complications and comorbidities in CAP

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SUMMARY: Cardiovascular complications and comorbidities in community-acquired pneumonia (CAP) are very frequent. Therefore, clinicians need to see CAP not as a simple accidental infection; rather, they should look at CAP patients as high-risk cardiovascular patients and thus diagnose and treat them in an appropriate way. Cardiac complications in the acute phase of CAP are most often seen in the first days of disease. Therefore, better monitoring, diagnostics and risk stratification in CAP with respect to cardiovascular diseases should be established. There is a higher long-term risk for cardiovascular events and mortality in CAP patients that has not been adequately recognised. Cardiovascular morbidity and mortality, especially in patients with known cardiovascular disease, might be reduced by influenza and pneumococcal vaccination.

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Community-acquired pneumonia (CAP) is the most common potentially fatal infectious disease throughout the western industrialised countries [1]. Despite the development of new antibiotics, the introduction of intensive care medicine and improved diagnostics, CAP still has a mortality rate of 5–15%, which is comparable to CAP mortality 60 years ago [2–5]. Interestingly, about 50% of CAP mortality within the first month is due to comorbidities and is not a direct consequence of CAP such as respiratory failure or sepsis [2]. Several investigations have consistently shown that long-term mortality is excessive after an acute phase of CAP compared to an age-matched cohort [6–11]. After 180 days the mortality rate is twice as high as the short-term mortality after 28 days. The highest impact of CAP on long-term mortality is in the first year after the initial CAP episode, but the association with excess long-term mortality can be demonstrated for at least 5 years. The main causes of death after a CAP episode are cardiovascular diseases and cancer, but chronic lower respiratory disease, renal failure and infection also play an important role [6–11]. In many patients who die in the longer term after CAP from cardiovascular disease, cancer and renal failure, the presence of these underlying diseases is unknown prior to the occurrence of CAP and even after the CAP episode. This supports the traditional hypothesis that in many cases, especially in the elderly, CAP might be a sentinel event for an underlying life-limiting disease [12]. The older the patients, the higher their risk for cardiovascular diseases [13].

In recent years there has been growing evidence that CAP and other respiratory infections might increase the risk for severe cardiovascular adverse events, including cardiovascular mortality.

Therefore, better knowledge about cardiovascular complications and comorbidities is highly important. Preventive measures to reduce cardiovascular events could lead to a reduction of the high mortality rate of CAP in the future. In this context, biomarkers might be helpful to detect patients at risk.

Clinical studies of cardiovascular complications in CAP

Incidence of cardiovascular complications in respiratory infections

Several epidemiological studies show a peak of cardiovascular mortality during the winter season [14]. In parallel, there is also a peak of lower respiratory tract infections in winter. The inflammation due to respiratory infections may increase fibrinogen levels, which results in pro-thrombotic vascular conditions that could trigger cardiovascular events [15, 16].

In three large studies in primary care, there was an increased risk for acute myocardial infarction or stroke within 90 days of a respiratory infection, with the highest risk directly after the infection and subsequent decrease over time [17–19]. In contrast to respiratory infections, urinary tract infections did not significantly increase the risk for cardiovascular events. Therefore, it is not an infection *per se* but the type of infection, which seems to play a major role. However, this association between respiratory infections and cardiovascular events is not necessarily causative. There are other risk factors, such as age, smoking and diabetes, which play a role for both respiratory infections and cardiovascular diseases.

Looking at the high long-term mortality in patients discharged from hospital after an episode of CAP, there are several studies showing cardiovascular events as the major cause for death [2, 9–11]. They show that cardiovascular mortality contributes to >30% of deaths at long-term follow-up (table 1).

Myocardial infarction

Many patients with acute myocardial infarction report respiratory infections in the days and weeks prior to infarction [27, 28]. In a multicentre study, there was a rate of 7.2% of CAP in patients admitted to hospital with an acute myocardial infarction [29]. Conversely, in an observational study with 170 patients hospitalised because of pneumococcal CAP, concurrent acute myocardial infarction was found in 7.1% of patients [20]. One major risk factor seems to be bacteraemia, which was found in 50% of patients with myocardial infarction. Those CAP patients with acute myocardial infarction had a 3.9-fold higher mortality risk. In the large Community-Acquired Pneumonia Organization (CAPO) database study with 500 CAP patients, acute myocardial

Table 1. Studies on cardiovascular complications in patients with community-acquired pneumonia

First author [ref.]	Patients n	Follow-up	Cardiovascular complications %	AMI %	Heart failure %	Arrhythmia %
Musher [20]	170	In hospital	19.4	7.1	14.7	5.9
Becker [21]	391	In hospital	17.4	7.9	12.3	2.8
Ramirez [22]	500	In hospital		5.8		
Corrales-Medina [23]	206	15 days		10.7		
Corrales-Medina [24]	2287	30 days	26.7 inpatients, 2.1 outpatients	1[#]	17.8[#]	5.9[#]
Perry [25]	50 119	30 days		1.2	9.1	8.4
Mandal [26]	4408	In hospital		3.2		9.3
Mortensen [7]	208	90 days	13[¶]			
Yende [9]	1799	1 year	33[¶]			
Johnstone [10]	3415	5.4 years	31[¶]			
Bruns [11]	356	7 years	16[¶]			

AMI: acute myocardial infarction. [#]: inpatients; [¶]: cardiovascular mortality.

infarction was diagnosed in 5.8% of patients [22]. The incidence of myocardial infarction was higher in those patients with more severe CAP (15%) and even higher in those CAP patients that were treated in the ICU (50%). In this study cohort, acute myocardial infarction was, with 28%, the second highest cause of treatment failure [30]. In a subgroup of patients with CAP due to *Streptococcus pneumoniae* or *Haemophilus influenzae*, the risk of a cardiovascular adverse event within 2 weeks was eight times higher compared to controls without CAP [23].

Cardiac arrhythmias

Antibiotic therapy might play a role in cardiovascular events, *e.g.* by QT-time prolongation and induction of arrhythmias. In patients with moderate or severe CAP, the combination of β-lactam antibiotics with macrolides reduces short-term mortality [31]. However, previous observational studies have suggested that cardiovascular events and mortality might be increased during treatment with macrolides [32, 33]. To study the safety of clarithromycin, two datasets of patients with respiratory infections were analysed [34]. One consisted of 1343 hospitalised patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and the second of 1631 patients with CAP. Over 1 year, there were 268 cardiovascular events in the AECOPD group and 171 in the CAP group. After adjustment, the use of clarithromycin as antibiotic therapy was associated with an increased risk of cardiovascular events in AECOPD (hazard ratio (HR) 1.50) and in CAP (HR 1.68). There was a significant association between clarithromycin use and cardiovascular mortality (HR 1.52) but not all-cause mortality in AECOPD, but no association between clarithromycin use in CAP and cardiovascular or all-cause mortality. Longer duration of clarithromycin therapy was associated with more cardiovascular events. Fluoroquinolones can also have effects on QT prolongation. In a comparative study of the three fluoroquinolones ciprofloxacin, levofloxacin and moxifloxacin, moxifloxacin caused the most pronounced QT prolongation through interactions with potassium channels [35]. In AECOPD there was no association of cardiovascular events and the use of β-lactam antibiotics or doxycycline.

In another observational Spanish study with 3921 CAP patients, the incidence of cardiovascular complications was studied [36]. During hospitalisation, 315 (8%) patients had one or more acute cardiac events (199 new-onset or worsening cardiac arrhythmias, 118 new-onset or worsening congestive heart failure and/or 30 myocardial infarction). In multivariate analysis, acute cardiac events were associated with age >65 years, chronic heart disease, chronic kidney disease, tachycardia, septic shock, multilobar pneumonia, hypoalbuminaemia and pneumococcal pneumonia.

In a large study with 1343 inpatients and 944 outpatients with CAP, the incidence and type of cardiovascular events (new or worsening heart failure, new or worsening arrhythmias, or myocardial infarction) within 30 days were evaluated [24]. Cardiac complications were very common and more frequent in inpatients (26.7%) compared with outpatients (2.1%). The majority of events (89.1% in inpatients, 75% in outpatients) were diagnosed within the first week, most of them within the first 24 hours. Risk factors for cardiovascular events were older age (OR 1.03), nursing home residence (OR 1.8), history of heart failure (OR 4.3), prior cardiac arrhythmias (OR 1.8), known coronary artery disease (OR 1.5), arterial hypertension (OR 1.5) and blood pH <7.35 (OR 3.2). After adjustment for CAP severity, cardiac complications were associated with increased risk of death at 30 days (OR 1.6). In inpatients, the most frequent cardiac complications were new or worsening heart failure (66.8%), new or worsening cardiac arrhythmias (22.1%) and myocardial infarction (3.6%).

Heart failure

New or worsening heart failure is the most frequent cardiac complication in CAP. In a meta-analysis, the incidence of heart failure was 14.1%, of acute coronary syndromes 5.3% and of cardiac arrhythmias 4.7% [37]. The incidence of heart failure as a consequence of CAP is more common in older populations and patients with pre-existing coronary artery disease, but not in those with higher prevalence of pre-existing congestive heart failure [37]. In females there is a

higher incidence of heart failure. The rate of all cardiac complications apart from incident heart failure is lower in studies of patients with higher prevalence of diabetes mellitus. Cardiac complications including incident heart failure are more common in studies with higher prevalence of chronic obstructive pulmonary disease.

Stroke

Several studies show that there may be an association between stroke and respiratory infections. ZURRÚ *et al.* [38] demonstrated that, in the year before stroke, infections were more frequent in stroke patients compared to controls (29% *versus* 13%, OR 2.6). The difference in infections between stroke patients and controls was only due to a difference in respiratory infections (19% *versus* 6%, OR 3.9), there was no difference in other types of infections. CAP was notably much more frequent in stroke patients than controls. In multivariable analysis adjusting for major vascular risk factors, respiratory infection was associated much more with stroke patients than controls (OR 4.9).

Pathophysiology of cardiovascular complications in respiratory infections

A summary of the pathophysiology of cardiovascular complications is shown in figure 1.

Atherosclerosis is an inflammatory disease [39]. The higher the levels of systemic measurable inflammatory markers (*e.g.* C-reactive protein (CRP), cytokines, coagulation parameters) in patients with atherosclerosis, the higher the risk for cardiovascular events and mortality [40–42]. Acute cardiovascular events, such as acute coronary syndrome or stroke, are the consequences of

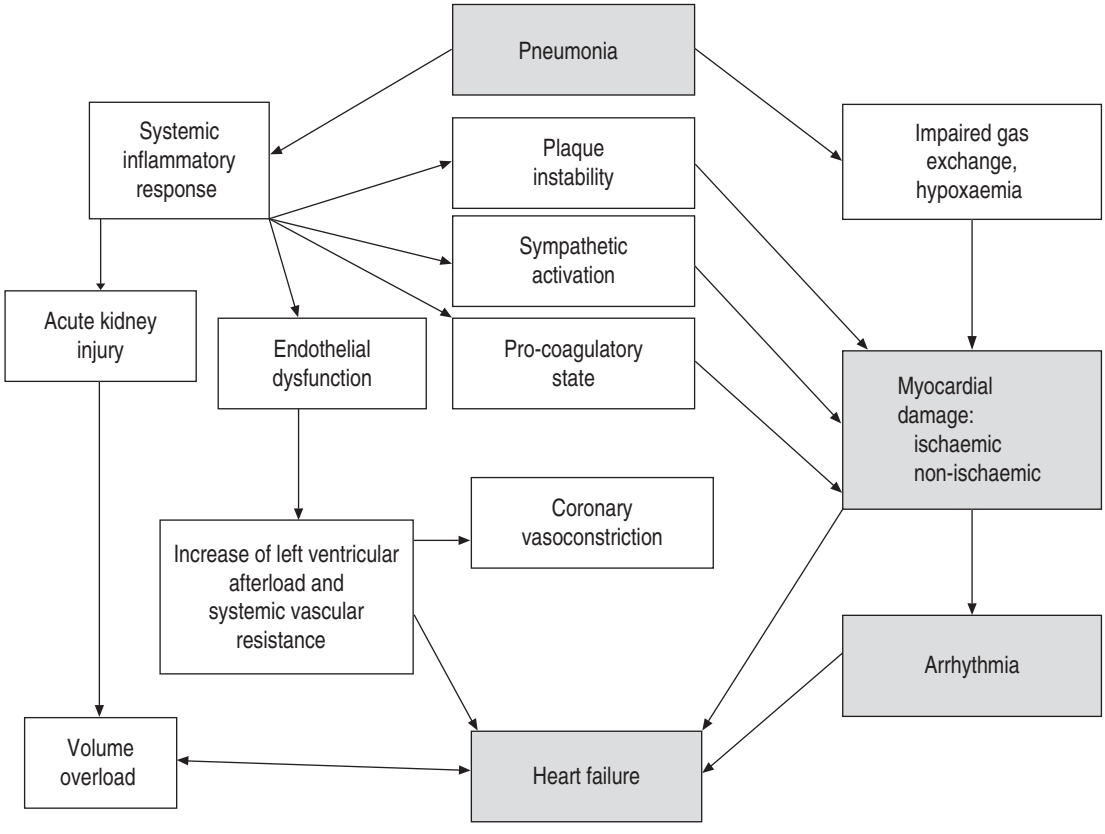

Figure 1. Pathophysiology of cardiovascular complications in patients with community-acquired pneumonia.

plaque rupture in an arterial vessel. Inflammatory stimuli can lead to the rupture of the stable fibrous cap of an atherosclerotic plaque. This leads to exposure of the lipid-rich core of the plaque, which induces platelet aggregation and local thrombus formation, resulting in acute occlusion of the vessel [39].

How can the higher rate of cardiovascular events in patients with respiratory infections be explained? Respiratory infections and especially CAP result not only in local inflammation in the lung but also in a significant systemic inflammatory response. There is a measurable systemic increase in inflammatory markers like CRP, interleukin (IL)-6, tumour necrosis factor-α and IL-8. Under effective treatment, these inflammatory markers decrease. However, even after clinical cure, a persisting subclinical inflammatory reaction can be measured. YENDE *et al.* [9] showed that higher levels of IL-6 and IL-10 at hospital discharge are associated with an increased mortality risk for the following year. This means that, due to an increased systemic inflammatory status, patients with respiratory infections are at risk of cardiovascular events not only during the acute phase of the infection but also for a longer period of time thereafter. This increased inflammatory reaction can trigger inflammation in formerly stable atherosclerotic plaques, which can eventually result in plaque rupture.

Platelet activation plays a major role in acute cardiovascular events. CAP induces platelet activation and leads to a pro-thrombotic status [43, 44]. In two studies, thrombocytosis was associated with poor outcome in CAP patients [45, 46]. It should be noted that, despite the presence of thrombocytosis, there were not more cardiac or ischaemic complications in CAP. Therefore, it is not clear if platelets alone were responsible for the worse outcome, or if thrombocytosis is a surrogate marker for severe systemic inflammation.

Another factor is the aggravation of endothelial dysfunction. As a result of endothelial activation, nitric oxide (NO) is released by the endothelium, especially by higher expression of inducible NO synthase. This leads to vasodilatation, myocardial dysfunction, vascular leakage and finally multiple organ failure, as in sepsis [47]. Other mediators, such as cyclooxygenase-2, prostanoids, endothelin-1 and von Willebrand factor, also play a role in the inflammatory cascade. The development of heart failure as a result of CAP can be explained by the deleterious inflammatory effects on the heart with resulting myocardial dysfunction, impaired myocardial contractility, higher myocardial oxygen demand and lower myocardial oxygen delivery [47]. However, CAP can result not only in sepsis but also in respiratory failure and hypoxaemia, which impairs myocardial oxygen delivery. The myocardial ischaemia may even result in myocardial necrosis with elevation of troponin.

Prevention of cardiovascular complications in CAP

Medical therapy

There are some observational studies in CAP patients that point to some potential positive effects of the drugs that are standard in the treatment of cardiovascular diseases. Statin therapy might reduce the short-term mortality in CAP patients due to pleiotropic effects, including immunomodulation and prevention of acute coronary syndromes by plaque stabilisation [47, 48]. Other pleiotropic properties of statins are anti-inflammatory and anti-oxidative effects, improvement of endothelial function, and increased NO bioavailability. Interestingly, the immunomodulatory effects of statins are independent of lipid lowering [49]. One main reason for death in patients with CAP in the acute phase is sepsis. There are several reports that show improved survival in sepsis patients pre-treated with statins. In a prospective cohort study in 361 patients with acute bacterial infections, a pre-treatment with statins was associated with a reduced rate of severe sepsis (19% in non-statin group *versus* 2.4% in statin group) and intensive care unit (ICU) admissions (12.2% in non-statin group *versus* 3.7% in statin group) [50]. In a very large observational study with 141 487 cardiovascular patients, it was shown that statin therapy

was associated with a decreased rate of sepsis (HR 0.81), severe sepsis (HR 0.83) and fatal sepsis (HR 0.75) [51].

Angiotensin-converting enzyme (ACE) inhibitors could also be beneficial for the reduction of cardiovascular mortality in CAP [52]. In a retrospective cohort study in 8652 hospitalised CAP patients aged $\geqslant$65 years, current statin use (OR 0.54) and ACE inhibitor use (OR 0.80) were significantly associated with decreased 30-day mortality. However, there is no reliable data about the effect of β-blockers on CAP survival. For anti-platelet drugs there is some preliminary data that in CAP the use of acetylsalicylic acid (ASA) and thienopyridines may reduce the need for intensive care treatment [53]. It could be beneficial to treat hospitalised CAP patients with ASA. There are some recent studies that found a protective effect of ASA in severe sepsis and septic shock [53, 54]. In a retrospective analysis of 886 septic patients who were admitted to the surgical ICU, it was shown that patients who were treated during the ICU stay with ASA (100 $mg \cdot day^{-1}$) had a significantly lower mortality, with an odds ratio of 0.57 (95% CI 0.39–0.83) for overall hospital mortality. In a subgroup analysis, clopidogrel resulted in a similar benefit to ASA, but the combination of ASA and clopidogrel failed to improve outcome.

Thus, better medical treatment of cardiovascular comorbidities offers the possibility of reducing mortality in CAP patients. Randomised controlled intervention trials in this field are warranted.

There are several studies suggesting that macrolides have beneficial effects for patients with respiratory infections, due to their immunomodulatory effects rather than their antimicrobial properties [55]. These immunomodulatory effects have been demonstrated in non-infectious immune-related diseases, *e.g.* asthma, chronic obstructive pulmonary disease, diffuse panbronchiolitis and bronchiectasis [56]. It was shown that macrolides modulate inflammatory cytokines in sepsis and CAP and that they can improve clinical outcome [31, 57].

Vaccination

The main prophylaxis for reduction of respiratory infections is vaccination. The two respiratory infections that can be effectively reduced by vaccination are influenza and pneumococcal disease. If there is a true link between respiratory infections and cardiovascular events, then vaccination has the potential to reduce both.

Regarding influenza, there are some studies showing that influenza vaccination leads to a reduction in myocardial infarction and stroke [58, 59]. The largest study is a recent multicentre study in 40 countries by JOHNSTONE *et al.* [60] of 31 546 high-risk patients aged $\geqslant$55 years and with known vascular disease, which looked at the combined primary end-point of death resulting from cardiovascular causes, myocardial infarction or stroke, during four influenza seasons (2003–2007). In the three seasons where circulating influenza matched the vaccine antigen, influenza vaccination was associated with a lower cardiovascular risk (OR 0.62, 0.69 and 0.52). In the season with an incomplete match between circulating influenza and the vaccine antigen, there was no association between influenza vaccination and outcome (OR 0.96). Surprisingly, the risk reduction was almost the same during the influenza season and the non-influenza season. For pneumococcal vaccination, however, there was no association between cardiovascular events and vaccination in any influenza season.

Regarding pneumococcal disease, the study results are conflicting. One reason might be that the polysaccharide vaccine, which has been used for adults in the past, is not as effective as the conjugate vaccine, which was mainly used for children over the last 10 years. A severe limitation is that there is no randomised controlled trial in the field of pneumococcal vaccination and subsequent cardiovascular morbidity and mortality.

In a case–control study with 999 patients with acute myocardial infarction, the likelihood of pneumococcal vaccination in those with infarction was significantly lower (OR 0.53) [61]. In contrast, a large prospective study with 84 170 patients showed no association between pneumococcal vaccination and acute myocardial infarction and stroke [62]. Another matched

case–control study with 16 012 patients with acute myocardial infarction could not find a protective effect of pneumococcal vaccination. However, in this study, influenza vaccination was protective (OR 0.81) [63].

A Chinese study was prospectively performed in patients that received influenza and pneumococcal vaccination. Interestingly, influenza and pneumococcal vaccination alone did not show a reduction in cardiovascular mortality, whereas patients with the dual influenza and pneumococcal vaccination had a significantly lower mortality for stroke (HR 0.67) and acute myocardial infarction (HR 0.52) [64].

Diagnostic algorithms

The established risk scores for CAP are the complicated Pneumonia Severity Index and the simple CRB65 score (confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, blood pressure $<$90 mmHg (systolic) or $\leqslant$60 mmHg (diastolic), age $\geqslant$65 years) [64, 65]. However, the scores are validated for the estimation of short-term mortality only. As already stated, there is an excess mortality in the longer term in patients surviving the acute phase of CAP. Many of these patients die from cardiovascular diseases. At present, there is no established diagnostic algorithm or score and no biomarker for the estimation of the long-term prognosis of CAP. There are no systematic studies evaluating the effect of routine ECG testing or echocardiography in CAP patients for the detection of cardiovascular comorbidities. However, ECG testing is of limited sensitivity and specificity for the diagnosis of heart failure, and routine echocardiography in all CAP patients seems not to be realistic for reasons of limited resources. Biomarker measurement as a screening test for the presence of heart failure or other structural heart disease would be very helpful. In recent years, there have been several biomarkers studied for short- and long-term prognosis in CAP.

In sub-studies by CAPNETZ (the German Competence Network for Community-Acquired Pneumonia), the value of new cardiovascular biomarkers for the prediction of long-term mortality at 180 days was evaluated. In the first study, 1740 patients with CAP were enrolled [66]. Pro-atrial natriuretic peptide (proANP), pro-vasopressin (copeptin), procalcitonin (PCT), CRP and CRB65 score were determined on admission. In patients who died within 28 and 180 days, proANP and copeptin levels were significantly higher compared to levels in survivors. In receiver operating characteristic analysis for 28- and 180-day survival, the areas under the curve (AUCs) for copeptin (0.84 and 0.78) and proANP (0.81 and 0.81) were superior to the AUCs for CRB65 score (0.74 and 0.71) and the inflammatory markers PCT, CRP and leukocytes. In multivariable Cox proportional hazards regression analyses adjusted for comorbidity and pneumonia severity, proANP and copeptin were independent and the strongest predictors of short- and long-term mortality. In a second CAPNETZ sub-study, the predictive potential of the new biomarkers proadrenomedullin (proADM), proANP, copeptin and pro-endothelin-1 (proET-1) was compared to inflammatory biomarkers PCT and CRP and the clinical severity score CRB65 for short-term and long-term mortality in patients with CAP on an intra-individual basis [67]. 728 patients were followed for 180 days. In patients who died within 28 and 180 days, proADM, proANP, copeptin, C-terminal proET-1 and PCT, as well as CRB-65, were significantly higher compared with survivors. In Cox regression analysis, proADM had the best performance for the prediction of 28- and 180-day survival. Midregional (MR)-proADM was independent of CRB65 score and added prognostic information for short- and long-term mortality. MR-proADM was an independent and strong predictor of short- and long-term mortality. There are other studies that had similar results with respect to proADM. In a study by Bello *et al.* [68], proADM was a good prognostic factor for mortality almost 1 year after discharge from hospital.

How can it be explained that cardiovascular biomarkers are better for the prediction of short- and long-term mortality compared to inflammatory biomarkers? The inflammatory markers PCT, CRP and leukocytes are predominantly useful for the diagnosis of infection, whereas the new cardiovascular biomarkers reflect different aspects of CAP. There are various underlying mechanisms for this phenomenon. First, all of these new cardiovascular markers are elevated in

sepsis, which is one of the main causes of short-term death in the acute phase of CAP. Secondly, copeptin, proANP, proET-1 and proADM are increased in patients with cardiac failure. The elevation of these biomarkers in CAP might be due to underlying pre-existing cardiac disease or septic cardiomyopathy. CAP may aggravate underlying previously unknown cardiovascular or renal disease due to acute inflammatory activation. The fact that proADM seems to be superior to the other cardiovascular markers (proANP, copeptin and proET-1) might be explained by the multiple functions of adrenomedullin. In contrast to ANP, arginine vasopressin and endothelin, which have predominantly cardiovascular actions, adrenomedullin possesses not only cardiovascular activity but also anti-inflammatory and antibacterial functions. The new cardiovascular biomarkers might become new and useful additional prognostic markers for short- and long-term risk assessment in CAP. Elevated levels of these new cardiovascular biomarkers in CAP identify a high-risk population. As a consequence, increased attention to possible cardiovascular disease, chronic lung disease and cancer and closer medical follow-up may be indicated. Whether this results in an improved long-term outcome in CAP patients remains to be evaluated in future prospective randomised controlled studies with inclusion of these new biomarkers into the treatment algorithm. A positive study with a biomarker-guided treatment algorithm would remarkably change the management of CAP patients.

Conclusions

Cardiovascular complications and comorbidities in CAP are very frequent. Therefore, clinicians need to see CAP not as a simple accidental infection, but should look at CAP patients as high-risk cardiovascular patients and diagnose and treat them in an appropriate way. Cardiac complications in the acute phase of CAP are most often seen in the first days of disease. Therefore, better monitoring, diagnostics and risk stratification in CAP with respect to cardiovascular diseases should be established. There is a long-term higher risk for cardiovascular events and mortality in CAP patients that has not been adequately recognised. Cardiovascular morbidity and mortality, especially in patients with known cardiovascular disease, might be reduced by influenza and pneumococcal vaccination.

Statement of Interest

S. Krüger has received personal fees for lectures and advisory board work from ThermoFisher (manufacturer of proADM and PCT) of less than €10 000, outside the submitted work.

References

1. World Health Organization. The Top Ten Causes of Death. www.who.int/mediacentre/factsheets/fs310.pdf Date last accessed: September 4, 2013. Date last updated: February 2007.
2. Mortensen EM, Coley CM, Singer DE, *et al.* Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Arch Intern Med* 2002; 162: 1059–1064.
3. File TM Jr, Marrie TJ. Burden of community-acquired pneumonia in North American adults. *Postgrad Med* 2010; 122: 130–141.
4. Fine MJ, Smith MA, Carson CA, *et al.* Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. *JAMA* 1996; 275: 134–141.
5. Waterer GW, Kessler LA, Wunderink RG. Medium-term survival after hospitalization with community-acquired pneumonia. *Am J Respir Crit Care Med* 2004; 169: 910–914.
6. Brancati FL, Chow JW, Wagener MM, *et al.* Is pneumonia really the old man's friend? Two-year prognosis after community-acquired pneumonia. *Lancet* 1993; 342: 30–33.
7. Mortensen EM, Kapoor WN, Chang CH, *et al.* Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. *Clin Infect Dis* 2003; 37: 1617–1624.
8. Koivula I, Sten M, Makela P. Prognosis after community-acquired pneumonia in the elderly: a population-based 12 year follow-up study. *Arch Intern Med* 1999; 159: 1550–1555.
9. Yende S, D'Angelo G, Kellum JA, *et al.* Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med* 2008; 177: 1242–1247.

10. Johnstone J, Eurich DT, Majumdar SR, *et al.* Long-term morbidity and mortality after hospitalization with community-acquired pneumonia: a population-based cohort study. *Medicine (Baltimore)* 2008; 87: 329–334.
11. Bruns AH, Oosterheert JJ, Cucciolillo MC, *et al.* Cause-specific long-term mortality rates in patients recovered from community-acquired pneumonia as compared with the general Dutch population. *Clin Microbiol Infect* 2011; 17: 763–768.
12. Yende S, Angus DC, Ali IS, *et al.* Influence of comorbid conditions on long term mortality after pneumonia in older people. *J Am Geriatr Soc* 2007; 55: 518–525.
13. Kannel WB, Gordan T. Evaluation of cardiovascular risk in the elderly: the Framingham study. *Bull NY Acad Med* 1978; 54: 573–591.
14. Keatinge WR, Donaldson GC. Cardiovascular mortality in winter. *Arctic Med Res* 1995; 54: Suppl. 2, 16–18.
15. Crawford VL, McNerlan SE, Stout RW. Seasonal changes in platelets, fibrinogen and factor VII in elderly people. *Age Ageing* 2003; 32: 661–665.
16. Woodhouse PR, Khaw KT, Plummer M, *et al.* Seasonal variations of plasma fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease. *Lancet* 1994; 343: 435–439.
17. Meier CR, Jick SS, Derby LE, *et al.* Acute respiratory-tract infections and risk of first-time acute myocardial infarction. *Lancet* 1998; 351: 1467–1471.
18. Smeeth L, Thomas SL, Hall AJ, *et al.* Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004; 351: 2611–2618.
19. Clayton TC, Thompson M, Meade TW. Recent respiratory infection and risk of cardiovascular disease: case–control study through a general practice database. *Eur Heart J* 2008; 29: 96–103.
20. Musher DM, Rueda AM, Kaka AS, *et al.* The association between pneumococcal pneumonia and acute cardiac events. *Clin Infect Dis* 2007; 45: 158–165.
21. Becker T, Moldoveanu A, Cukierman T, *et al.* Clinical outcomes associated with the use of subcutaneous insulin-by-glucose sliding scales to manage hyperglycemia in hospitalized patients with pneumonia. *Diabetes Res Clin Pract* 2007; 78: 392–397.
22. Ramirez J, Aliberti S, Mirsaeidi M, *et al.* Acute myocardial infarction in hospitalized patients with community-acquired pneumonia. *Clin Infect Dis* 2008; 47: 182–187.
23. Corrales-Medina VF, Serpa J, Rueda AM, *et al.* Acute bacterial pneumonia is associated with the occurrence of acute coronary syndromes. *Medicine* 2009; 88: 154–159.
24. Corrales-Medina VF, Musher DM, Wells GA, *et al.* Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. *Circulation* 2012; 125: 773–781.
25. Perry TW, Pugh MJ, Waterer GW, *et al.* Incidence of cardiovascular events after hospital admission for pneumonia. *Am J Med* 2011; 124: 244–251.
26. Mandal P, Chalmers JD, Choudhury G, *et al.* Vascular complications are associated with poor outcome in community-acquired pneumonia. *QJM* 2011; 104: 489–495.
27. Spodick DH, Flessas AP, Johnson MM. Association of acute respiratory symptoms with onset of acute myocardial infarction: prospective investigation of 150 consecutive patients and matched control patients. *Am J Cardiol* 1984; 53: 481–482.
28. Clayton TC, Capps NE, Stephens NG, *et al.* Recent respiratory infection and the risk of myocardial infarction. *Heart* 2005; 91: 1601–1602.
29. Lichtman JH, Fathi A, Radford MJ, *et al.* Acute, severe noncardiac conditions in patients with acute myocardial infarction. *Am J Med* 2006; 119: 843–850.
30. Aliberti S, Amir A, Peyrani P, *et al.* Incidence, etiology, timing, and risk factors for clinical failure in hospitalised patients with community-acquired pneumonia. *Chest* 2008; 134: 955–962.
31. Restrepo MI, Mortensen EM, Waterer GW, *et al.* Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. *Eur Respir J* 2009; 33: 153–159.
32. Ray WA, Murray KT, Meredith S, *et al.* Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 2004; 351: 1089–1096.
33. Wayne RA, Murray KT, Hall K, *et al.* Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012; 366: 1881–1890.
34. Schembri S, Williamson PA, Short PM, *et al.* Cardiovascular events after clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies. *BMJ* 2013; 346: f1235.
35. Tsikouris JP, Peeters MJ, Cox CD, *et al.* Effects of three fluoroquinolones on QT analysis after standard treatment courses. *Ann Noninvasive Electrocardiol* 2006; 11: 52–56.
36. Viasus D, Garcia-Vidal C, Manresa F, *et al.* Risk stratification and prognosis of acute cardiac events in hospitalized adults with community-acquired pneumonia. *J Infect* 2013; 66: 27–33.
37. Corrales-Medina VF, Suh KN, Rose G, *et al.* Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. *PLoS Med* 2011; 8: e1001048.
38. Zurrú MC, Alonzo C, Brescacín L, *et al.* Recent respiratory infection predicts atherothrombotic stroke: case-control study in a Buenos Aires healthcare system. *Stroke* 2009; 40: 1986–1990.
39. Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999; 340: 115–126.
40. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation* 2003; 107: 363–369.

41. Pai JK, Pischon T, Ma J, *et al.* Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med* 2004; 351: 2599–2610.
42. Curb JD, Abbott RD, Rodriguez BL, *et al.* C-reactive protein and the future risk of thromboembolic stroke in healthy men. *Circulation* 2003; 107: 2016–2020.
43. Yeaman MR. Platelets in defense against bacterial pathogens. *Cell Mol Life Sci* 2010; 67: 525–544.
44. Kellum JA, Kong L, Fink MP, *et al.* Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. *Arch Intern Med* 2007; 167: 1655–1663.
45. Mirsaeidi M, Peyrani P, Aliberti S, *et al.* Thrombocytopenia and thrombocytosis at time of hospitalization predict mortality in patients with community-acquired pneumonia. *Chest* 2010; 137: 416–420.
46. Prina E, Ferrer M, Ranzani OT, *et al.* Thrombocytosis is a marker of poor outcome in community-acquired pneumonia. *Chest* 2013; 143: 767–775.
47. Merx MW, Weber C. Sepsis and the heart. *Circulation* 2007; 116: 793–802.
48. Chalmers JD, Short PM, Mandal P, *et al.* Statins in community acquired pneumonia: evidence from experimental and clinical studies. *Respir Med* 2010; 104: 1081–1091.
49. Kwak B, Mulhaupt F, Myit S, *et al.* Statins as a newly recognized type of immunomodulator. *Nat Med* 2000; 6: 1399–1402.
50. Almog Y, Shefer A, Novack V, *et al.* Prior statin therapy is associated with a decreased rate of severe sepsis. *Circulation* 2004; 110: 880–885.
51. Hackam DG, Mamdani M, Li P, *et al.* Statins and sepsis in patients with cardiovascular disease: a population-based cohort analysis. *Lancet* 2006; 367: 413–418.
52. Mortensen EM, Pugh MJ, Copeland LA, *et al.* Impact of statins and angiotensin-converting enzyme inhibitors on mortality of subjects hospitalised with pneumonia. *Eur Respir J* 2008; 31: 611–617.
53. Winning J, Reichel J, Eisenhut Y, *et al.* Anti-platelet drugs and outcome in severe infection: clinical impact and underlying mechanisms. *Platelets* 2009; 20: 50–57.
54. Otto GP, Sossdorf M, Boettel J, *et al.* Effects of low-dose acetylsalicylic acid and atherosclerotic vascular diseases on the outcome in patients with severe sepsis or septic shock. *Platelets* 2013; 24: 480–485.
55. Amsden GW. Anti-inflammatory effects of macrolides – an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? *J Antimicrob Chemother* 2005; 55: 10–21.
56. Schultz MJ. Macrolide activities beyond their antimicrobial effects: macrolides in diffuse panbronchiolitis and cystic fibrosis. *J Antimicrob Chemother* 2004; 54: 21–28.
57. Parnham MJ. Immunomodulatory effects of antimicrobials in the therapy of respiratory tract infections. *Curr Opin Infect Dis* 2005; 18: 125–131.
58. Naghavi M, Barlas Z, Siadaty S, *et al.* Association of influenza vaccination and reduced risk of recurrent myocardial infarction. *Circulation* 2000; 102: 3039–3045.
59. Keller T, Weeda VB, van Dongen CJ, *et al.* Influenza vaccines for preventing coronary heart disease. *Cochrane Database Syst Rev* 2008; 3: CD005050.
60. Johnstone J, Loeb M, Teo KK, *et al.* Influenza vaccination and major adverse vascular events in high-risk patients. *Circulation* 2012; 126: 278–286.
61. Lamontagne F, Garant MP, Carvalho JC, *et al.* Pneumococcal vaccination and risk of myocardial infarction. *CMAJ* 2008; 179: 773–777.
62. Tseng HF, Slezak JM, Quinn VP, *et al.* Pneumococcal vaccination and risk of acute myocardial infarction and stroke in men. *JAMA* 2010; 303: 1699–1706.
63. Siriwardena AN, Gwini SM, Coupland CA. Influenza vaccination, pneumococcal vaccination and risk of acute myocardial infarction: matched case-control study. *CMAJ* 2010; 182: 1617–1623.
64. Hung IF, Leung AY, Chu DW, *et al.* Prevention of acute myocardial infarction and stroke among elderly persons by dual pneumococcal and influenza vaccination: a prospective cohort study. *Clin Infect Dis* 2010; 51: 1007–1016.
65. Lim WS, van der Eerden MM, Laing R, *et al.* Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003; 58: 377–382.
66. Krüger S, Ewig S, Kunde J, *et al.* Pro-atrial natriuretic peptide and pro-vasopressin for predicting short-term and long-term survival in community-acquired pneumonia. Results from the German Competence Network, CAPNETZ. *Thorax* 2010; 65: 208–214.
67. Krüger S, Ewig S, Giersdorf S, *et al.* Cardiovascular and inflammatory biomarkers to predict short- and long-term survival in community-acquired pneumonia. Results from the German Competence Network, CAPNETZ. *Am J Respir Crit Care Med* 2010; 182: 1426–1434.
68. Bello S, Lasierra AB, Mincholé E, *et al.* Prognostic power of proadrenomedullin in community-acquired pneumonia is independent of aetiology. *Eur Respir J* 2012; 39: 1144–1155.

Chapter 20

Pneumococcal and influenza vaccination

Mathias W. Pletz[*] *and Tobias Welte*[#]

SUMMARY: Pneumococci are the most frequent pathogen in community-acquired pneumonia (CAP). Influenza is the most important virus for more severe upper and lower respiratory tract infection, including CAP. Animal and epidemiological studies have revealed synergistic effects between these two pathogens. Complimentary cohort studies have confirmed synergistic protective effects of both the influenza and pneumococcal vaccines.

Currently, two types of pneumococcal vaccines are in clinical use, the pneumococcal polysaccharide vaccine (PPSV) and the pneumococcal conjugate vaccine (PCV). Data regarding efficacy against nonbacteraemic pneumonia in adults are conflicting (PPSV) or pending (PCV). Data from different countries demonstrate that PCV serotypes can be reduced in the whole population by vaccination of children, who are the main reservoir of pneumococci (herd protection).

Beside the classical trivalent influenza split vaccine, several novel influenza vaccine types have been released during the last decade, such as a live attenuated vaccine for children, a cell culture-derived vaccine for patients with egg protein allergy and a tetravalent vaccine covering the two major influenza B lines.

This chapter discusses the advantages and disadvantages of different vaccine types available for pneumococcus and influenza.

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For decades, most studies investigating the aetiology of community-acquired pneumonia (CAP) have identified *Streptococcus pneumoniae* as the most frequent pathogen [1–3].

Influenza is the most important virus for more severe upper and lower respiratory tract infection, including CAP. VON BAUM *et al.* [4] found influenza in 12% of patients with defined aetiology enrolled into the German cohort study on CAP (German Competence Network for Community-Acquired Pneumonia (CAPNETZ)). In autumn and winter, the incidence was even higher (16.2% of patients with defined aetiology) [4].

In vitro, animal experiment-based and clinical data suggest a clinically relevant synergism between pneumococci and influenza virus, which are both, at least in part, vaccine-preventable pathogens. This chapter will discuss the pros and cons of the different vaccination strategies against these two pathogens, with the major focus on pneumococci.

Vaccine recommendations regarding indication, risk groups and prioritisation differ slightly between individual countries. A summary is presented in figures 1 and 2.

Pneumococcal vaccine

Bacteriology and epidemiology

Streptococcus pneumoniae is a major pathogen causing CAP, acute exacerbations of chronic bronchitis, meningitis, sinusitis and otitis media. Pneumococcal diseases can be distinguished as invasive and noninvasive (fig. 3). Invasive pneumococcal disease (IPD) is defined as the isolation of *S. pneumoniae* from a normally sterile site, such as blood, cerebrospinal fluid or pleural fluid.

Noninvasive disease (*i.e.* sinusitis or otitis media) is frequent but not severe; invasive diseases are associated with a high case fatality rate but a lower incidence. Pneumococcal pneumonia can be invasive (*i.e.* positive blood or pleural culture in 10–15% of cases) or noninvasive (detection in respiratory specimens only). In contrast to other noninvasive diseases (sinusitis and otitis media), the mortality rate for nonbacteraemic pneumococcal CAP is still considerable and does not always differ from invasive pneumococcal disease [3, 12]. There is uncertainty as to how to classify pneumococcal pneumonias detected by urine antigen test only. However, pneumococcal pneumonia represents the main burden of pneumococcal disease, since it has a high case fatality rate (~15% of hospitalised patients) and a high incidence [3, 13].

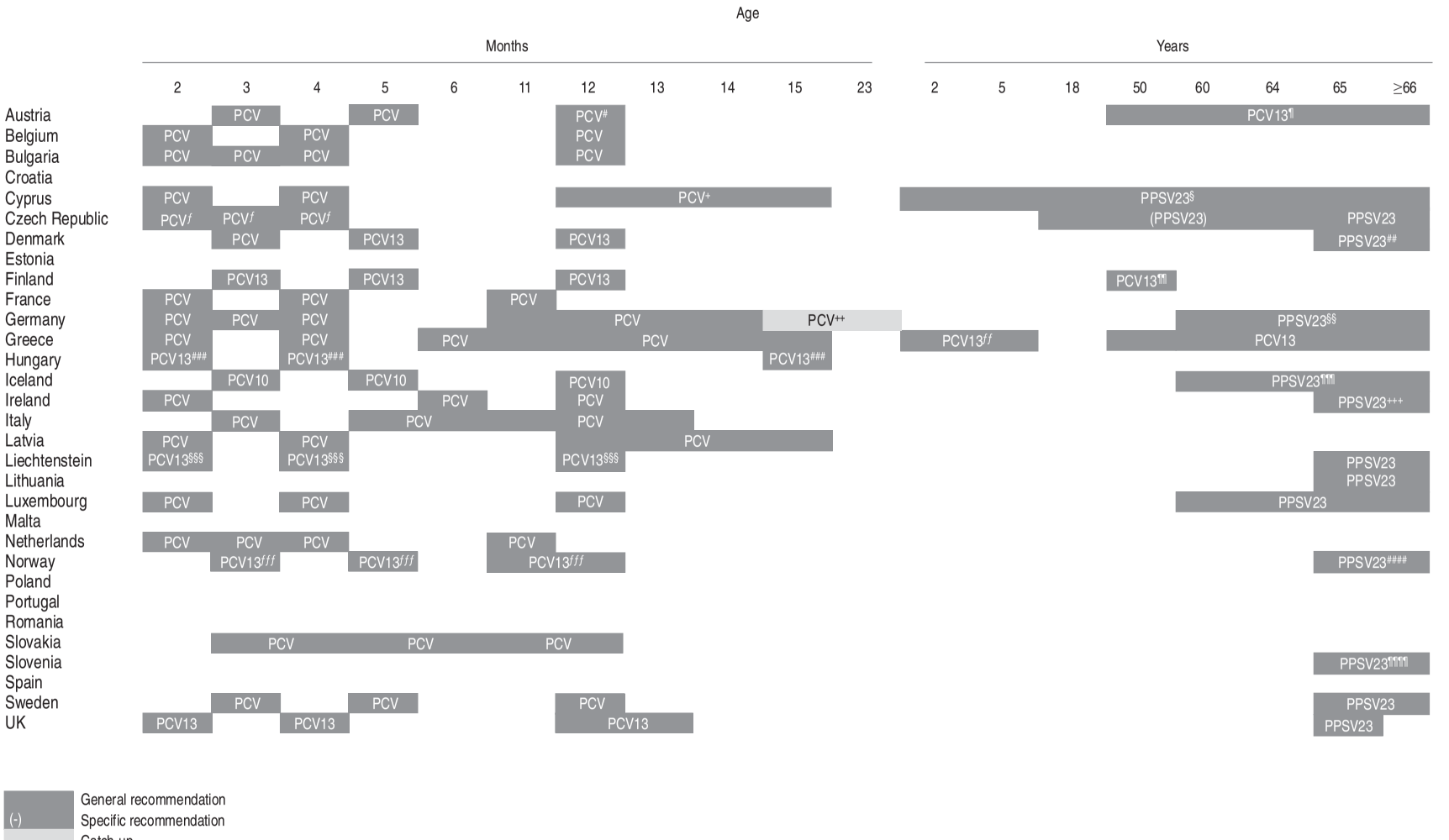
Pneumococcal infections usually involve infants, the immunocompromised and the elderly. The main reservoir of pneumococci is the nasopharyngeal zone of healthy carriers, especially infants. Up to 70% of infants attending day-care centres and more than 90% of infants in some native communities [14] but less than 5% of adults are colonised [14–16].

Similar to other encapsulated bacteria (*e.g.* meningococci and *Haemophilus influenzae* type B), pneumococci protect themselves from phagocytosis by a polysaccharide capsule, which is poorly recognised by phagocytes. Killing of pneumococcus requires antibodies binding to capsule polysaccharides and initiating opsonophagocytosis. Compared with proteins, polysaccharides are much less immunogenic, as most T-cells do not recognise polysaccharides. Although vaccine development was started as early as the 1940s, the poor immunogenicity of capsule polysaccharides was the main obstacle for the development of an effective vaccine. In addition, more than 90 pneumococcal serotypes are known and there is no or only limited cross-immunity.

Not all pneumococcal serotypes occur with the same frequency and the spectrum of serotypes is not the same in different areas of the world. In general, the spectrum of serotypes is more diverse in adults than children and less diverse in IPD than non-IPD. This may be explained, at least, in part by different immunogenicity of the different capsular types, by increased fitness of some clones (genotypes) that express certain serotypes and is probably also influenced by the circulating influenza strains. Changes in pneumococcal epidemiology had already occurred before the introduction of pneumococcal conjugate vaccine (PCV) and cannot always be sufficiently explained. A Danish surveillance study observing seven decades of IPD described substantial temporal changes within the pneumococcal serotype spectrum even before the introduction of PCVs [17]. The polysaccharide capsule also determines the affinity for the respiratory epithelium [14]. In most studies, serotypes 6A, 6B, 19F and 23F were identified as serotypes causing frequent nasopharyngeal colonisation but rarely invasive disease [18]. However, mortality for less invasive serotypes is similar to invasive serotypes in some studies, probably because less invasive serotypes tend to infect patients with more comorbidities or genetic predisposition (*e.g.* mannose-binding lectin deficiency) [12, 19].

Available pneumococcal vaccines

Currently, there are two different vaccine types against pneumococci in clinical use: pneumococcal polysaccharide vaccine (PPSV) and PCV. Whereas PPSV tries to compensate for the poor


Age
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General recommendation
(-) Specific recommendation
Catch-up

Figure 1. Recommended immunisations for pneumococcal disease. PCV: polysaccharide conjugate vaccine; PPSV: pneumococcal polysaccharide vaccine. [#]: earliest, 6 months after the second dose. [¶]: if no previous vaccination, one dose of PPSV23 after 1 year; if previous vaccination with PPSV23, one dose of PCV13 2 years later; if previous dose of PCV13, one dose of PPSV23 2 years later; recommended but not free of charge. [+]: catch-up possible until 6 years if previous recommended doses were missed. [§]: vaccines only given for specific indications. [ƒ]: PCV vaccines can be administered simultaneously with hexavalent vaccine or separately during the first year of life; three doses at 1-month intervals. [##]: PCV13 also recommended; for recommendations from Statens Serum Institut (Copenhagen, Denmark) for vaccination of people at risk, refer to [5]; there are no official recommendations from the Danish Health and Medicines Authority (Copenhagen) for use of PPSV23 or PCV13 but there is reimbursement for defined at-risk groups. [¶¶]: recommended but not free of charge; for more information, please refer to [6]. [++]: number of doses necessary varies according to age. [§§]: one dose recommended; booster only for specific indications; [ƒƒ]: only for children previously vaccinated with a PCV7- or PCV10-containing vaccine. [###]: nonmandatory vaccination and free of charge for children under 2 years of age. [¶¶¶]: one dose every 10 years (every 5 years for those with conditions putting them at risk of severe disease). [+++]: vaccine is free but administration fees may be charged to patient (based on income and eligibility for free healthcare). [§§§]: not part of the basic vaccination plan. [ƒƒƒ]: PCV13 replaced PCV7 on April 11, 2011. [####]: one dose if not vaccinated in the previous 10 years. [¶¶¶¶]: PCV13 can be used; not free of charge; further information on pneumococcal disease vaccination policy available at [7]. Data from [8], the contents of which are covered by the European Centre for Disease Prevention and Control legal notice [9].

immunogenicity of polysaccharides by including large amounts of antigen, in PCV, every polysaccharide is conjugated with a highly immunogenic protein (*e.g.* diphtheria toxoid protein CRM197 or tetanus toxoid protein). After vaccination with PCV, B-cells bind and internalise the polysaccharide–protein conjugate *via* a polysaccharide-specific receptor and subsequently present the processed protein component *via* major histocompatibility complex class II molecules to effector T-cells that are specific for the particular protein component (fig. 4). In conclusion, conjugating the polysaccharides with protein induces T-cell support that results in antibody isotype switching, the generation of memory B-cells and an increase in antibody avidity. In contrast, the PPSV-induced immune response is limited to B-cells and, therefore, lacks some of these features, particularly the generation of memory B-cells. PPSV was not licensed for vaccination in children <2 years of age, because the immature immune system shows a very poor reaction to pure polysaccharide antigens. However, in a recent study in Mexican children between 18 months and 4 years of age, PPSV induced antibodies in all age groups [21].

PPSV contains polysaccharides of 23 pneumococcal serotypes (table 1). The first PCV contained protein-conjugated polysaccharides of seven serotypes (PCV7) and was first released in 2000 in the USA for vaccination of children up to 2 years of age. In the following years, several other countries started to implement PCV7 in their vaccination programme, some as late as 2007 (in Germany). In 2009, a 10-valent PCV was licensed for the vaccination of children. In 2010, the manufacturer of PCV7 (Pfizer, New York, NY, USA) replaced it with an extended version, PCV13.

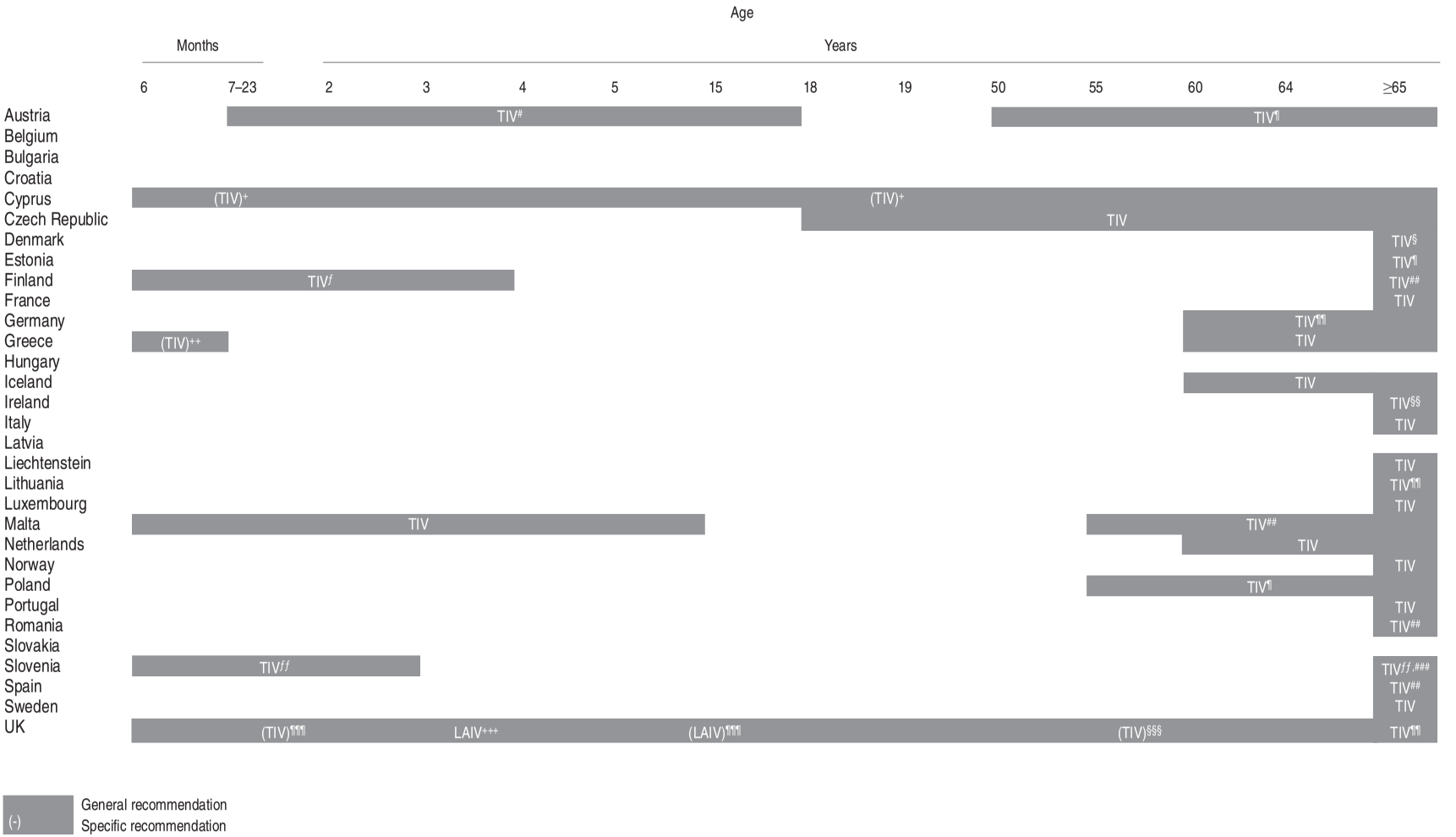
Initially, all PCVs were licensed for use in children between 2 months and 2 years of age. In 2011, PCV13 was licensed by the European Medicines Agency for adults >50 years of age. In 2012–2013, Pfizer successfully applied for licenses in additional age groups and, since 2013, PCV13 has been licensed for all ages >2 months.

Mucosal immunity and hyporesponsiveness

PPSV23 covers more serotypes that PCV13 but has the following immunological disadvantages.

Lack of mucosal immunity

Whereas PCV has been shown to reduce the carrier rate in vaccinated children by several studies [22, 23], similar studies for PPSV have shown no effect [24, 25]. Also, sequential vaccination (PCV followed by PPSV) in children reduced only the carrier rate for the serotypes contained in PCV, whereas the additional serotypes in PPSV were not affected [26].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(TIV)§§§
General recommendation
(-) Specific recommendation

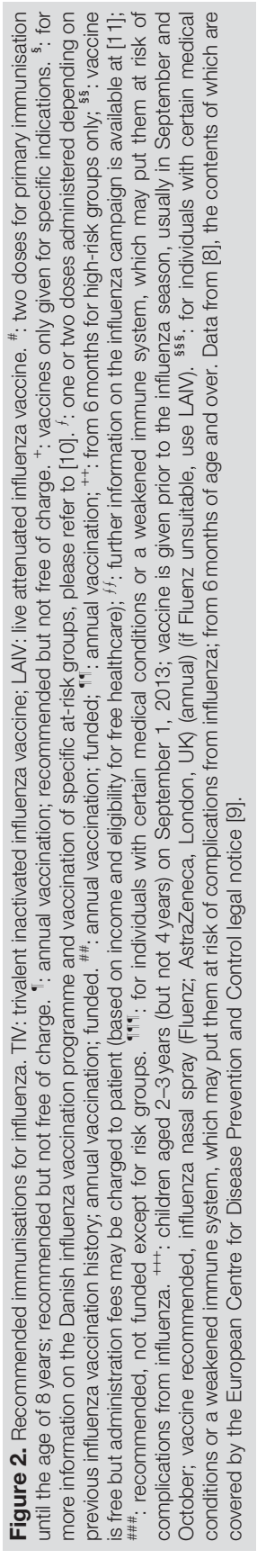

Figure 2. Recommended immunisations for influenza. TIV: trivalent inactivated influenza vaccine; LAIV: live attenuated influenza vaccine. #: two doses for primary immunisation until the age of 8 years; recommended but not free of charge. ¶: annual vaccination; recommended but not free of charge. +: vaccines only given for specific indications. §: for more information on the Danish influenza vaccination programme and vaccination of specific at-risk groups, please refer to [10]. f: one or two doses administered depending on previous influenza vaccination history; annual vaccination; funded. ##: annual vaccination; funded; ¶¶: annual vaccination; ++: from 6 months for high-risk groups only; §§: vaccine is free but administration fees may be charged to patient (based on income and eligibility for free healthcare); ff: further information on the influenza campaign is available at [11]; ###: recommended, not funded except for risk groups. ¶¶¶: for individuals with certain medical conditions or a weakened immune system, which may put them at risk of complications from influenza. +++: children aged 2–3 years (but not 4 years) on September 1, 2013; vaccine is given prior to the influenza season, usually in September and October; vaccine recommended, influenza nasal spray (Fluenz; AstraZeneca, London, UK) (annual) (if Fluenz unsuitable, use LAIV). §§§: for individuals with certain medical conditions or a weakened immune system, which may put them at risk of complications from influenza; from 6 months of age and over. Data from [8], the contents of which are covered by the European Centre for Disease Prevention and Control legal notice [9].

Hyporesponsiveness

PPSV induces hyporesponsiveness (like other polysaccharide vaccines, *e.g.* meningococcal polysaccharide vaccine) [27]. This means a prior vaccination with PPSV attenuates consecutive vaccination with PPSV or PCV. This effect is probably caused by a massive stimulation of pre-existing antipneumococcal memory B-cells and naïve B-cells. CLUTTERBUCK *et al.* [28] detected pneumococcus-specific memory B-cells in 86% of a group of elderly (>70 years of age), which is probably a result of former colonisation or infections. These cells become plasma cells, which later die without leaving memory cells. The differentiation into memory B-cells is T-cell-dependent but polysaccharides do not induce a T-cell response [29]. This results in a pneumococcus-specific depletion of the B-cell pool. Particularly in older individuals, the generation of novel naïve B-cells and, therefore, the effect of hyporesponsiveness last longer. Hyporesponsiveness is one of the reasons why most national committees on vaccination have withdrawn the initial recommendation for repeating PPSV vaccination every 5 years.

The degree of hyporesponsiveness seems to depend on the interval between the vaccinations (and probably also on the age of the vaccinated individual) and was not detected 10 years after prior PPSV vaccination [30].

In contrast, PCV induces memory B-cells, as was shown in elderly adults by CLUTTERBUCK *et al.* [28], and antibody responses to a second vaccination with PCV or PPSV were similar to those after the first PCV vaccination (*i.e.* no hyporesponsiveness) [27, 31].

PCV-induced herd protection effects and replacement

Herd protection effect and antimicrobial resistance

The widespread vaccination of infants, the main reservoir of pneumococci, reduces not only the incidence of invasive infections in the vaccinated population but also the proportion of colonised children, at least for the seven or 13 covered serotypes (fig. 5). The decrease in colonised children subsequently interrupts the typical infection chain between infants and parents or infants and grandparents, and therefore protects unvaccinated adults [32].

According to population-based epidemiological studies, invasive pneumococcal infections by the 13 vaccine serotypes have been reduced by 94% in all age groups and almost eradicated in children [32, 33]. Herd protection effects have not been described for PPSV.

In the early 1990s, surveillance studies detected a sudden increase in penicillin- and macrolide-resistant pneumococci [34–37]. The main drivers of this increase were permanent selective pressure by a worldwide increasing usage of antibiotics and the expansion of some multidrug-resistant pneumococcal clones [38]. These clones combine resistance with higher growth rates, which may explain the successful spreading [39].

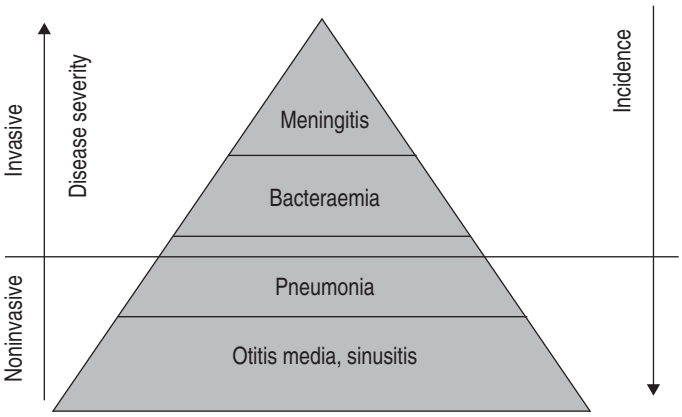

Figure 3. The spectrum of pneumococcal diseases. Pneumonia represents the main burden; it is frequent and severe.

Clones do not equal serotypes but genotypes and are defined by identical or similar multilocus sequence typing patterns. Clones are even able to switch serotypes under selective pressure, such as that induced by the vaccine. Several studies have detected that the rise in antibiotic-resistant serotype 19A after introduction of PCV7 can be partly explained by capsular switching from multiresistant clones with other serotypes, that are contained in PCV 7, to 19A [40]. Currently, most antibiotic-resistant pneumococcal clones exhibit serotypes that are contained in PCV13 and are therefore reduced [41–44].

The opposite effects of increased antimicrobial usage and the herd protection effects of PCV can be summarised as follows. Resistant clones expressing vaccine serotypes are diminished while resistance rates within nonvaccine serotypes continue to increase [42]. In Germany, macrolide resistance in IPD peaked in 2005 (32% in children and 19% in adults) and decreased to 15% and 13%, respectively, in 2008, only 18 months after implementation of PCV7 [45]. Similar observations were made in the USA. In contrast, a current Canadian study reported a rise in multidrug-resistant pneumococci due to the rise of serotype 19A, which is now contained in PCV13, after the introduction of PCV7 (*i.e.* replacement, see later) [46].

Replacement

Currently, herd protection effects have substantially reduced the total incidence of invasive pneumococcal disease; however, the remaining infections, in children and in adults, are almost completely caused by serotypes not contained in PCV13. This phenomenon is called "replacement" and is an issue of intensive global epidemiological research. The current extent of replacement seems to depend on the duration of the vaccination programme with PCV13 and is more pronounced in children than in adults. 19A has been reported as the most important replacement serotype after introduction of PCV7 and was therefore included in PCV13.

A recent model from the US Centers for Disease Control and Prevention (CDC), which aimed to predict the effects of PCV13 while taking into account the lessons learned about replacement after introduction of PCV7, predicted rates of IPD in children under 5 years of age decreasing from 21.9 to 9.3 cases per 100 000 population. The authors concluded that the amount of serotype replacement is unlikely to greatly affect the overall number of cases prevented by PCV13 [47]. Other experts argue that replacement after introduction of PCV13 will be similar to that seen after PCV7 and that vaccination of adults with PCV13 is therefore unneeded, because vaccination of children with PCV13 will result in an almost complete eradication of these 13 serotypes within a decade [48].This argument is plausible but it also has to be considered that 1) many cases of IPD and probably non-IPD can be prevented until these 13 serotypes are eradicated, and 2) the potential for spreading/replacement of non-PCV13 serotypes is currently unknown. According to an ongoing surveillance study in Germany, in 2013, 50% of all IPDs in adults are caused by PCV13 serotypes; a PCV13 vaccination programme for infants was started in the beginning of 2010.

However, a non-serotype-specific pneumococcal vaccine is needed. Such a vaccine would be able to resolve the issues of replacement or different serotype distribution within different regions. The current research on protein-based pneumococcal vaccines is promising [49, 50].

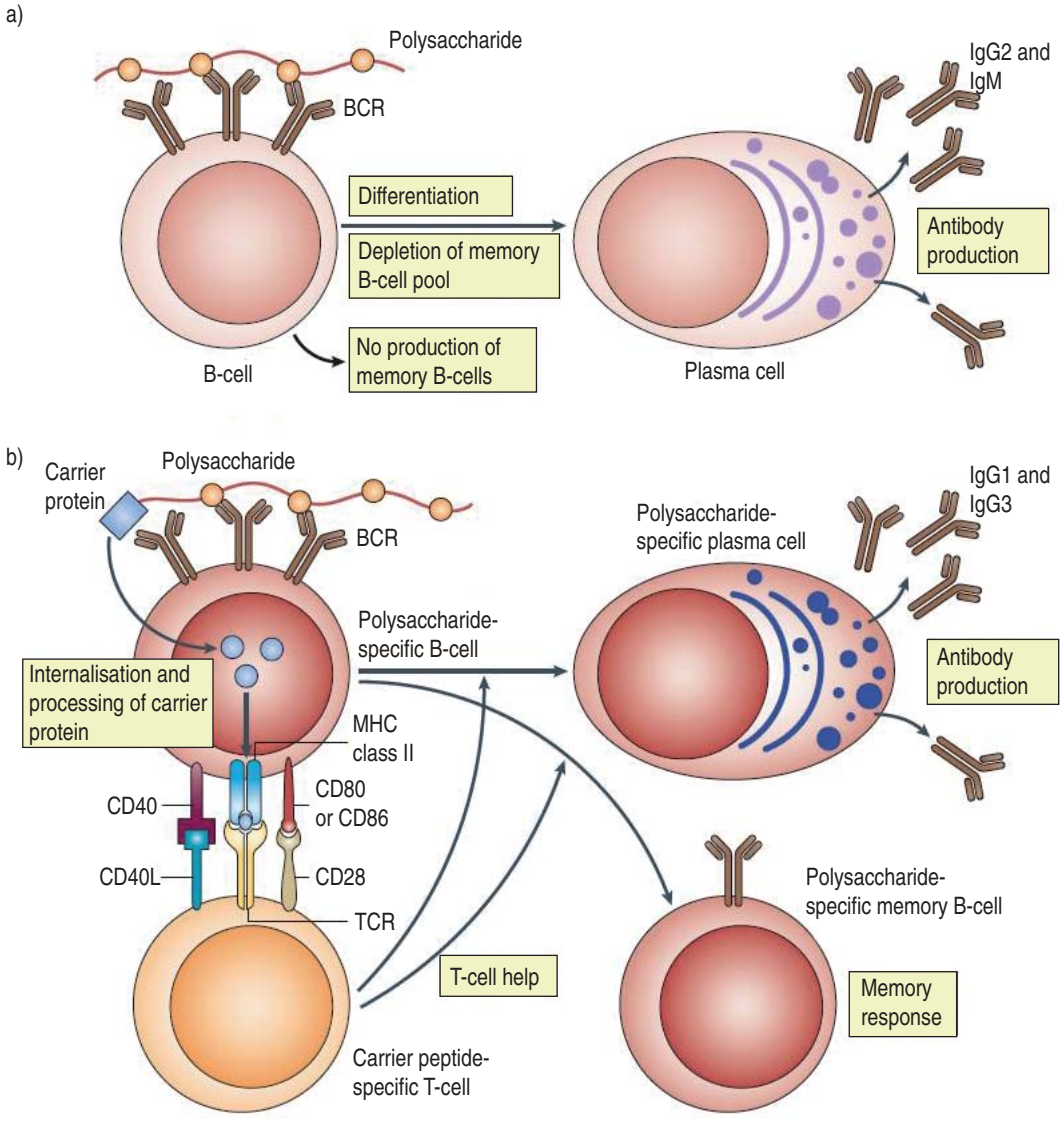

Figure 4. The immune response to polysaccharide and protein–polysaccharide conjugate vaccines. a) Polysaccharides from the encapsulated bacteria that cause disease in early childhood stimulate B-cells by cross-linking the B-cell receptor (BCR) and drive the production of immunoglobulins. This process results in a lack of production of new memory B-cells and a depletion of the memory B-cell pool, such that subsequent immune responses are decreased. b) The carrier protein from protein–polysaccharide conjugate vaccines is processed by the polysaccharide-specific B-cell, and peptides are presented to carrier peptide-specific T-cells, resulting in T-cell help for the production of both plasma cells and memory B-cells. MHC: major histocompatibility complex; CD40L: CD40 ligand; TCR: T-cell receptor. Reproduced from [20] with permission from the publisher.

The role of PPSV and PCV in the prevention of pneumonia

As outlined earlier, most studies addressing the efficacy of pneumococcal vaccines addressed IPD. The first placebo-controlled, double-blind randomised controlled trial (RCT) addressing the efficacy of PCV13 against pneumococcal pneumonia in adults is currently being conducted in the Netherlands. The primary objective of the CAPITA trial (Community Acquired Pneumonia Immunization Trial in Adults) is to establish the efficacy in the prevention of a first episode of vaccine serotype-specific pneumococcal CAP in 85 000 community-dwelling adult persons aged 65 years and older [51]. The database for this trial was locked in

Table 1. Serotype coverage of pneumococcal vaccines

Serotype	PCV7[#]	PCV10[¶]	PCV13[§]	PSV[ƒ]
1		+	+	+
2				+
3			+	+
4	+	+	+	+
5		+	+	+
6A			+	
6B	+	+	+	+
7F		+	+	+
8				+
9N				+
9V	+	+	+	+
10A				+
11A				+
12F				+
14	+	+	+	+
15B				+
17F				+
18C	+	+	+	+
19A			+	+
19F	+	+	+	+
20				+
22F				+
23F	+	+	+	+
33F				+

Pneumococcal conjugate vaccine (PCV)7 is no longer available and was replaced by PCV13. PPSV: pneumococcal polysaccharide vaccine; +: serotype covered by PCV. [#]: Prevnar (Pfizer, New York, NY, USA); [¶]: Synflorix (GlaxoSmithKline, Brentford, UK); [§]: Prevnar 13 (Pfizer); [ƒ]: Pneumovax (Merck, Whitehouse Station, NJ, USA).

autumn 2013. At the time of writing, statistical analysis is ongoing and publication is expected in 2014.

To date, the results on the efficacy of PPSV in clinical studies are conflicting. A recent Cochrane meta-analysis of RCTs found that there was efficacy against all-cause pneumonia in low-income (OR 0.54, 95% CI 0.43–0.67) but not high-income countries. PPSV was not associated with substantial reductions in all-cause mortality (OR 0.90, 95% CI 0.74–1.09). However, PPSV reduced the risk of all IPD, with a pooled estimated odds ratio of 0.26 (95% CI 0.14–0.45); that is, a protective vaccine efficacy of 74% (95% CI 55–86%) [52]. Interestingly, the odds ratio of 0.27 for IPD in vaccinated *versus* unvaccinated patients could be reproduced by a large cohort study [3].

Similar to the Cochrane meta-analysis, an earlier meta-analysis found that PPSV efficacy in studies was lower in studies with adequate concealment of allocation [53]. In fact, there is only one recent adequate RCT that found a significant reduction in pneumococcal pneumonia by 63.8% (95% CI 32.1–80.7%) and all-cause pneumonia by 44.8% (95% CI 22.4–60.8%) but no significant reduction in nonpneumococcal pneumonia. In addition, none of the vaccinated patients who developed pneumococcal pneumonia died, compared to a 37% death rate for pneumococcal pneumonia in the unvaccinated group. This study was conducted in 1006 Japanese nursing home residents (mean age 85 years) and not funded by industry. Surveillance was performed for 1000 days and there was no difference in death from any cause [54].

To date, there are only few RCTs addressing the clinical efficacy of PCV, which was released much later than PPSV. All RCTs were conducted in children. One study found a significant reduction of acute otitis media after vaccination with PCV10 [55]. A RCT from South Africa found that vaccination with PCV9 significantly reduced the incidence of radiologically

confirmed pneumonia and also reduced the incidence of vaccine-serotype and antibiotic-resistant invasive pneumococcal disease among children with and those without HIV infection [56].

There is no head-to-head study comparing PCV and PPSV clinical efficacy in adults. However, two RCTs with similar designs conducted by the same principal investigator in a similar setting (HIV-infected African adults) that compared the efficacy against IPD have been published. FRENCH and co-workers [57, 58] could not find any efficacy for PPSV but a 74% (95% CI 30–90%) efficacy for PCV7 for included serotypes (hazard ratio (HR) 0.26, 95% CI 0.10–0.70).

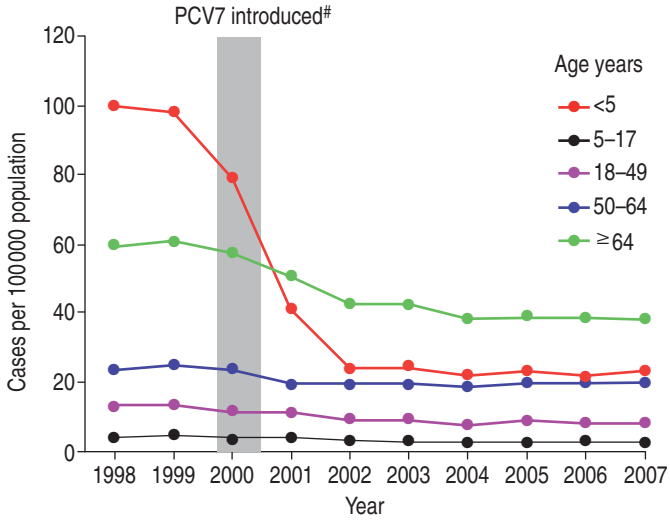

Figure 5. Changes in overall invasive pneumococcal disease incidence rates by age group, 1998–2007. PCV: pneumococcal conjugate vaccine. #: PCV7 was introduced in the USA for routine use among young children and infants in the second half of 2000. Reproduced from [32] with permission from the publisher.

Does sequential PCV-PPSV vaccination have a role?

In conclusion, there are two pneumococcal vaccines available for adults: PPSV23, which protects only from invasive disease but has broader serotype coverage; and PCV-13, which probably protects from noninvasive pneumococcal pneumonia and has proven effectiveness by substantial changes of pneumococcal epidemiology. In theory, sequential vaccination of both vaccines, first PCV then PPSV to prevent hyporesponsiveness, should provide superior protection against the 13 PCV serotypes and at least partial protection against the additional 11 serotypes in PPSV23. This strategy was tested in regard to antibody response in several RCTs and has been proposed by several experts in the field [59–62]. In 2013, the American College for Immunization Practices (ACIP) proposed sequential vaccination for individuals at increased risk for pneumococcal disease [63]. Currently, there are no studies proving clinical utility and the optimal interval is unknown. The ACIP suggests at least 8 weeks.

Influenza vaccine

Virology

Influenza viruses are encapsulated, single-stranded RNA viruses. They are classified as type A, B or C according to their core proteins. Influenza viruses have a broad range of hosts, including other mammals and birds. Influenza A is considered to be more virulent than influenza B. Influenza C epidemics in young children have been reported; however, human influenza C infections are rare. Vaccination is only available against influenza A and B. The envelope proteins haemagglutinin (H) and neuraminidase (N) are the main targets of neutralising antibodies. Influenza A is subtyped according to the combination of haemagglutin (nine known variants) and neuraminidase (16 variants). To date, the most common subtypes of influenza A consist of H1, H2 or H3, and N1 or N2.

Because the viral RNA polymerase is not error-checking, influenza virus (particularly influenza A) has a mutation rate 300 times higher than that of other microbes [64]. Accumulation of point

mutations results in ''antigenic drift'', which enables influenza to evade the annually acquired immunity in humans. ''Antigenic shift'' occurs only in influenza A and is the re-assortment that can occur when two strains infect the same host, mostly pigs. The resulting chimeric virus can be the cause of a pandemic.

Influenza vaccine strategies

Similar to pneumococcal disease, young children, the elderly, patients with comorbidities and the immunocompromised suffer the highest influenza-related morbidity and mortality. National recommendations for vaccination differ, particularly regarding the vaccination of young children.

According to a recent meta-analysis, during pregnancy, females were at higher risk for hospital admission, and those in the last trimester and those who were less than 4 weeks *post partum* had significantly increased mortality When compared with those in the first or second trimester, females in the third trimester had an increase in all-cause mortality (OR 1.22, 95% 1.01–1.48; inconsistency 0%; n=5) [65]. The World Health Organization (WHO) perspective regarding influenza vaccination is given in table 2 and also includes pregnant females as a risk group. Some countries recommend vaccination of pregnant females only in the second and third trimesters. The ACIP recently recommended vaccination of all pregnant females [67].

Similar to pneumococci, far-spread vaccination of young children can confer herd protection. For example, from 1962 to 1994, a vaccination programme for schoolchildren was launched in Japan. During this period, mortality attributable to pneumonia and influenza in individuals >65 years of age decreased from one to 0.4 cases per 100 000 *per annum* and all-cause mortality decreased by 37 000 to 49 000 deaths per year. Mortality rose again after the programme had been abandoned. A model published by REICHELT *et al.* [68] calculated that one death was prevented for every 420 schoolchildren vaccinated. Since the 2010–2011 influenza season, the CDC has recommended that all persons should be immunised annually against influenza, starting from the age of 6 months, which is the youngest age for which any influenza vaccine is approved [69].

Influenza vaccination plays a crucial role in controlling pandemics. Because vaccine access is expected to be limited during the early response to a pandemic, ethical vaccine distribution plans for within-country and global allocation are necessary [70].

Available influenza vaccines

There are three types of seasonal influenza vaccine available: inactivated influenza vaccines (*e.g.* trivalent inactivated influenza vaccine (TIV)); the live attenuated influenza vaccine (LAIV); and the recombinant egg-protein-free vaccine.

Live attenuated vaccine

LAIV is administered intranasally. The contained viruses are adapted to cold, which allows replication in the slightly cooler temperature of the nasopharyngeal mucosa but prevents viraemia or lower respiratory tract infection. A meta-analysis comparing TIV with LAIV concluded that LAIV seems to be slightly more effective than TIV in children [71]. Studies comparing TIV with LAIV in adults have shown conflicting results, probably because the accumulating influenza immunity in adults may prevent local replication of the vaccine virus [72].

Table 2. Influenza vaccine recommendations: World Health Organization (WHO) perspective

WHO recommends annual vaccination for (in order of priority):
1) nursing-home residents (the elderly or disabled)
2) people with chronic medical conditions
3) elderly individuals
4) other groups such as pregnant females, healthcare workers, those with essential functions in society and children from ages 6 months to 2 years

Information from [66].

Tri- and quadrivalent vaccines

Both TIV and LAIV contain three influenza strains (two influenza A and one influenza B strain). The specific composition is annually recommended by the WHO. Influenza B mutates two to three times slower than A and antigenic shift has not been observed in influenza B. Consequently, influenza B is less genetically diverse, with only one influenza B serotype. Since the 1970s, influenza B viruses have diverged into two antigenically distinct virus lineages called Yamagata and Victoria by accumulation of point mutations [73]. According to miss-match between the recommended and the predominantly circulating influenza B lineage, the vaccine efficacy can be as low as 31%, as described for the 2011–2012 season in Taiwan [74]. Recently, quadrivalent inactivated influenza virus (QIV) and quadrivalent LAIV have been licensed and are recommended by the WHO, when available. Studies have confirmed superior immunogenicity for the additional influenza B strain without interfering with immune responses to shared strains in adults and children [75, 76]. It has been estimated that availability of QIV from 1999 to 2009 could have reduced annual cases (range 2200–970 000), hospitalisations (range 14–8200) and deaths (range 1–485) in the USA [77].

Egg protein-free influenza vaccine

An influenza vaccine that is produced without the use of eggs, preservatives (*e.g.* thimerosal, a mercury derivative) or antibiotics was licensed in 2013 and is recommended for persons with egg allergy by the ACIP [78]. This vaccine contains recombinant haemagglutinin of the three recommended influenza strains.

Influenza vaccine in the elderly and the immunocompromised

Immune response in the elderly, particularly in the frail elderly, is inferior to that in younger adults. Different strategies have been investigated to address this problem: 1) adding an adjuvant (*e.g.* MF59); 2) increasing the dose (60 instead of 15 μg [79]) or using multiple doses; and 3) intradermal injection using a special microinjector [80].

The rationale for the microinjector is based on the fact that the dermis contains more antigen-presenting dendritic cells than subcutaneous or muscular tissue. In clinical studies, intradermal injection resulted in comparable or higher antibody titres [81]. In a study in nursing home residents, MF59-adjuvanted influenza vaccine induced greater and broader immune responses in elderly people with chronic conditions than conventional split vaccines [82]. However, in a study investigating the immunogenicity of a MF59-adjuvanted TIV in elderly chronic obstructive pulmonary disease patients, antibody titres (geometric mean) to A/H1N1 and A/H3N2 returned to baseline after 24 weeks. Therefore, even an adjuvanted vaccine may not provide protection in these patients when it is administered too far in advance of the influenza season [83].

Similarly to the elderly, immunogenicity is decreased in immunocompromised patients and strategies as outlined above have been studied in a heterogeneous cohort with inconsistent results [84]. Immunogenicity is tremendously decreased in transplant recipients. In a recent meta-analysis, ECKERLE *et al.* [85] describe conflicting results for multiple- *versus* single-dose vaccination in solid organ transplant (SOT) recipients. Nevertheless, they found that almost all trials observed a measurable vaccine response at least in a subset of SOT recipients after single-dose vaccination. Another, earlier meta-analysis on this issue concluded that, considering the hazard/benefit-ratio, it is advantageous to vaccinate immunocompromised patients [86].

Influenza vaccine and pneumonia

Reports of influenza causing excess mortality are mainly based on surveillance data and statistical models associating excess mortality in winter with influenza activity. Only very few reports addressed influenza in CAP, and reported mortality rates do not seem to support excess mortality in the presence of influenza-associated pneumonia, at least for seasonal influenza [4], so it is not surprising that there are no RCTs addressing the prevention of pneumonia by influenza vaccination. However, meta-analyses of mainly observational studies show that vaccination with

TIV of elderly nursing-home residents is associated with significant reductions in pneumonia by 53% (95% CI 35–66%) and 46% (95% CI 30–58%), respectively [87, 88]. In contrast, two more recent Cochrane meta-analyses found protection against laboratory-confirmed influenza but not pneumonia in healthy children and adults [89, 90].

Non-RCTs have shown effects of the influenza vaccine on pneumonia severity and outcome: TESSMER *et al.* [91] used the data from the observational, multicentre German cohort study (CAPNETZ) on CAP and analysed patients separately as an influenza season and off-season cohort. In the season cohort (2368 patients), CAP in vaccinated patients was significantly less severe according to the CURB (confusion, urea >7 mmol·L^{-1}, respiratory rate ≥ 30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) or ≤ 60 mmHg (diastolic)) index and these patients showed a significantly better overall survival within the 6-month follow-up period (HR 0.63, 95% CI 0.45–0.89). Within the off-season cohort (2632 patients), there was no significant influence of influenza vaccination status on CAP severity or outcome.

Adverse effects of the influenza vaccine

Probably because of the annually repeated mass vaccination against influenza, adverse events of the vaccine are discussed very negatively by the general public. Most of the prejudices against the vaccine were not supported in well-controlled analysis. In particular, adjuvanted vaccines have been accused of inducing autoimmune diseases, exacerbation of autoimmune diseases (*e.g.* in multiple sclerosis) and rejection in organ transplant recipients. Concerns about the potential for influenza vaccine to cause these adverse effects come from two types of evidence: case reports and small case series on the one hand, and basic science studies of alloimmunity on the other [92]. However, recent studies suggest that even the adjuvanted pandemic influenza vaccine has no clinically important effect on the production of autoantibodies in patients with rheumatic diseases [93]. Similarly, a meta-analysis addressing multiple sclerosis did not find any effect of influenza vaccine on the incidence or exacerbation of this disease [94].

Similarly, there is no clear evidence for induction of rejection by influenza vaccines in transplant recipients, although one study observed that some patients developed new anti-human leukocyte antigen antibodies post-vaccination [95]. Nevertheless, current guidelines strongly recommend yearly influenza vaccine starting 3 months after SOT (the delay is because of efficacy not safety concerns, but may be waived during an outbreak) [93, 96]. One large study showed an association between influenza vaccination and lower risk of allograft dysfunction and death [97]. In summary, it seems that actual influenza infection itself, rather than the vaccine, carries a risk of allograft dysfunction or autoimmune disease [93].

Synergism between pneumococcal and influenza vaccine

The synergism between pneumococci and influenza (*e.g.* secondary bacterial pneumonia) has been confirmed *in vitro*, in animal studies and by epidemiological data [4, 98–100]. An animal study found that influenza virus neuraminidase strips sialic acid from the lung, thus exposing receptors for pneumococcal adherence [101]. Recent studies showed that the presence of pneumococci enhances viral release from infected cells, that bacterial titres increase due to alveolar macrophage impairment and that co-infection is associated with a loss of lung repair [98, 100]. Therefore, synergism between pneumococcal and influenza vaccines should be expected [102]. Indeed, there are some studies confirming the benefit of combining both vaccines. The benefit of the combined use of PPSV23 with TIV for public health is supported by one of the largest intervention studies ever performed: between 1995 and 1998, among all Stockholm residents >65 years of age (n=259 627), 100 242 individuals were vaccinated against pneumococcal and influenza viral infections. Subsequently, hospitalisations occurring from December 1998 to May 1999 were recorded. Fewer cases of pneumonia were observed in the immunised group. Overall mortality was lower by 57% (95% CI 55–60%) in the vaccine group compared with nonvaccinees (15.1 *versus* 34.7 deaths per 1000 residents; $p<0.0001$) [103, 104].

It has been shown for both PCV13 and PPSV23 that they can be safely administered simultaneously with TIV without clinically relevant reduction of immunogenicity [105, 106].

Future developments

The main disadvantages of the current PCV are replacement and regional differences in pneumococcal serotype distribution. Currently, four strategies are exploited to overcome these obstacles [107]: 1) adaptations or modifications of the conjugate vaccine (*i.e.* extending serotype coverage or designing specific PCV for specific areas); 2) protein-based "universal" vaccines (see later); 3) a hybrid approach, whereby a conserved pneumococcal protein would be used as a carrier for a limited number of polysaccharides; and 4) a whole-cell approach.

Different serotype-independent protein targets are under investigation, such as pneumococcal surface protein PspA and choline-binding protein CbpA. Recombinant PspA has been safely administered to humans in a phase I clinical trial and found to be highly immunogenic. Other conserved and well-characterised virulence factors include pneumolysin, a cholesterol dependent cytolysin, and pneumococcal surface adhesin PsaA. A phase I study investigating three recombinant, avirulent *Salmonella typhi* strains each expressing *S. pneumoniae* surface PspA was recently completed (ClinicalTrials.gov identifier NCT01033409) [108].

The whole-cell approach has been investigated since the beginning of the century. However, modern modification, such as using avirulent, non-encapsulated strains with more accessible surface proteins, or genetic engineering by introduction of Toll-like receptor (TLR)4-activating targets, is promising [107].

Other research efforts aim for a universal influenza vaccine to avoid annual vaccination and possibly protect from future pandemics. Several different approaches have reached early phases of clinical development. VAX102 is a recombinant fusion protein that links four copies of the ectodomain of influenza virus matrix protein 2 antigen *to Salmonella typhimurium* flagellin, a TLR5 ligand. VAX102 has been successfully tested in a phase I trial [109] and a phase II trial has been completed (ClinicalTrials.gov identifier NCT00921947). FP-01.1 vaccine is under investigation (phase I, ClinicalTrials.gov identifier NCT01265914) and is another approach using a mixture of synthetic peptides. The peptide sequences, derived from internal influenza A proteins, were selected based on the presence of $CD4^+$ and $CD8^+$ T-cell epitopes and a high degree of conservation across all influenza strains, using a proprietary bioinformatics approach. Multimeric-001 (phase I) contains conserved linear epitopes from the haemagglutinin, nucleoprotein and matrix-1 proteins of influenza A and B strains, and is expected to protect against seasonal and pandemic influenza virus strains, regardless of mutations [110].

Conclusion

Pneumococci are typically transmitted from children to adults. The vaccination of children with PCV has caused tremendous changes in epidemiology of pneumococcal serotypes and decreased the rate of IPD in adults due to herd protection effects. The seven serotypes covered by the initially introduced PCV have been almost eradicated in the USA, which has started the PCV7 vaccination programme earlier (2000) than most countries. Briefly, after the introduction of PCV7 it became clear that remaining IPD cases are caused by nonvaccine serotypes (replacement). Therefore, extended conjugate vaccines (PCV10 and PCV13) were developed that covered most replacement serotypes, particularly 19A (PCV13 only). Currently, the extent of a second replacement phenomenon to PCV13, which was released only 3 years ago, remains unclear. PCV13 has been licensed for use in adults since 2011 and, in contrast to PPV23, is believed to protect from nonbacteraemic pneumonia. However, clinical data supporting this assumption are lacking and are currently being addressed in the Dutch CAPITA study, the results of which are expected to be published within the next few months.

Studies have shown that influenza and pneumococcal vaccines may provide synergistic protection. Several novel influenza vaccine formulations are available that aim for increased coverage (*i.e.* TIV), increased perception (*i.e.* LAIV administered intranasally to children) and increased immunogenicity (*i.e.* intradermal vaccines, adjuvanted vaccines and increased dosage of vaccines).

Data regarding transplant recipients show a decreased immunogenicity. However, according to most meta-analyses, the benefits of the influenza vaccine far outweigh its risk and, for example, the risk of rejection after organ transplantation is much higher after influenza infection than after influenza vaccination.

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Statement of Interest

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References

1. Woodhead M. Community-acquired pneumonia in Europe: causative pathogens and resistance patterns. *Eur Respir J* 2002; 20: Suppl. 36, 20s–27s.
2. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax* 2012; 67: 71–79.
3. Pletz MW, von Baum H, van der Linden M, *et al.* The burden of pneumococcal pneumonia – experience of the German competence network CAPNETZ. *Pneumologie* 2012; 66: 470–475.
4. von Baum H, Schweiger B, Welte T, *et al.* How deadly is seasonal influenza associated pneumonia? The German Competence Network for Community-acquired pneumonia (CAPNETZ). *Eur Respir J* 2011; 37: 1151–1157.
5. Statens Serum Institut. Pneumococcal vaccination of persons at increased risk of invasive pneumococcal disease. www.ssi.dk/English/News/EPI-NEWS/2012/No%2051b%20-%202012.aspx Date last updated: December 19, 2012.
6. Rokottajan Käsikirja. Pneumokokkikonjugaattirokotukset (PCV) [Pneumococcal conjugate vaccine (PCV)]. www.thl.fi/fi_FI/web/rokottajankasikirja-fi/pneumokokkikonjugaattirokotukset
7. IVZ. Cepljenje proti pnevmokoknim okužbam za odrasle in otroke [Vaccination against pneumococcal infection in adults and children]. www.ivz.si/cepljenje/strokovna_javnost/navodila_in_priporocila?pi=18&_18_view=item&_18_newsid=2230&pl=253-18.0 Date last updated: September 18, 2013.
8. European Centre for Disease Prevention and Control. Vaccine schedule. http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx Date last accessed: September 29, 2013.
9. European Centre for Disease Prevention and Control. Legal notice. http://ecdc.europa.eu/en/pages/legalnotice.aspx
10. Statens Serum Institut. Influenzavaccination [Influenza vaccination]. www.ssi.dk/Vaccination/Influenzavaccination.aspx Date last updated: September 25, 2013.
11. IVZ. Cepljenje proti gripi v sezoni 2013/2014 [Vaccination in the season 2013/2014]. www.ivz.si/cepljenje/strokovna_javnost/navodila_in_priporocila?pi=18&_18_view=item&_18_newsid=1316&pl=253-18.0 Date last updated: September 30, 2013.
12. Pletz MW, Welte T, Klugman KP. The paradox in pneumococcal serotypes: highly invasive does not mean highly lethal. *Eur Respir J* 2010; 36: 712–713.
13. Ewig S, Birkner N, Strauss R, *et al.* New perspectives on community-acquired pneumonia in 388 406 patients. Results from a nationwide mandatory performance measurement programme in healthcare quality. *Thorax* 2009; 64: 1062–1069.
14. Bogaert D, De Groot R, Hermans PW. *Streptococcus pneumoniae* colonisation: the key to pneumococcal disease. *Lancet Infect Dis* 2004; 4: 144–154.
15. Roca A, Hill PC, Townend J, *et al.* Effects of community-wide vaccination with PCV-7 on pneumococcal nasopharyngeal carriage in the Gambia: a cluster-randomized trial. *PLoS Med* 2011; 8: e1001107.

16. Putnam SD, Gray GC, Biedenbach DJ, *et al.* Pharyngeal colonization prevalence rates for *Streptococcus pyogenes* and *Streptococcus pneumoniae* in a respiratory chemoprophylaxis intervention study using azithromycin. *Clin Microbiol Infect* 2000; 6: 2–8.
17. Harboe ZB, Benfield TL, Valentiner-Branth P, *et al.* Temporal trends in invasive pneumococcal disease and pneumococcal serotypes over 7 decades. *Clin Infect Dis* 2010; 50: 329–337.
18. Brueggemann AB, Griffiths DT, Meats E, *et al.* Clonal relationships between invasive and carriage *Streptococcus pneumoniae* and serotype- and clone-specific differences in invasive disease potential. *J Infect Dis* 2003; 187: 1424–1432.
19. Valles X, Roca A, Lozano F, *et al.* Serotype-specific pneumococcal disease may be influenced by mannose-binding lectin deficiency. *Eur Respir J* 2010; 36: 856–863.
20. Pollard AJ, Perrett KP, Beverley PC. Maintaining protection against invasive bacteria with protein-polysaccharide conjugate vaccines. *Nat Rev Immunol* 2009; 9: 213–220.
21. Espinosa-Padilla SE, Murata C, Estrada-Parra S, *et al.* Immunogenicity of a 23-valent pneumococcal polysaccharide vaccine among Mexican children. *Arch Med Res* 2012; 43: 402–405.
22. Dagan R, Givon-Lavi N, Zamir O, *et al.* Reduction of nasopharyngeal carriage of *Streptococcus pneumoniae* after administration of a 9-valent pneumococcal conjugate vaccine to toddlers attending day care centers. *J Infect Dis* 2002; 185: 927–936.
23. Millar EV, O'Brien KL, Watt JP, *et al.* Effect of community-wide conjugate pneumococcal vaccine use in infancy on nasopharyngeal carriage through 3 years of age: a cross-sectional study in a high-risk population. *Clin Infect Dis* 2006; 43: 8–15.
24. Herva E, Luotonen J, Timonen M, *et al.* The effect of polyvalent pneumococcal polysaccharide vaccine on nasopharyngeal and nasal carriage of *Streptococcus pneumoniae. Scand J Infect Dis* 1980; 12: 97–100.
25. Russell FM, Carapetis JR, Satzke C, *et al.* Pneumococcal nasopharyngeal carriage following reduced doses of a 7-valent pneumococcal conjugate vaccine and a 23-valent pneumococcal polysaccharide vaccine booster. *Clin Vaccine Immunol* 2010; 17: 1970–1976.
26. Veenhoven RH, Bogaert D, Schilder AG, *et al.* Nasopharyngeal pneumococcal carriage after combined pneumococcal conjugate and polysaccharide vaccination in children with a history of recurrent acute otitis media. *Clin Infect Dis* 2004; 39: 911–919.
27. de Roux A, Schmole-Thoma B, Siber GR, *et al.* Comparison of pneumococcal conjugate polysaccharide and free polysaccharide vaccines in elderly adults: conjugate vaccine elicits improved antibacterial immune responses and immunological memory. *Clin Infect Dis* 2008; 46: 1015–1023.
28. Clutterbuck EA, Lazarus R, Yu LM, *et al.* Pneumococcal conjugate and plain polysaccharide vaccines have divergent effects on antigen-specific B cells. *J Infect Dis* 2012; 205: 1408–1416.
29. Pletz MW, Maus U, Krug N, *et al.* Pneumococcal vaccines: mechanism of action, impact on epidemiology and adaption of the species. *Int J Antimicrob Agents* 2008; 32: 199–206.
30. Musher DM, Manoff SB, McFetridge RD, *et al.* Antibody persistence ten years after first and second doses of 23-valent pneumococcal polysaccharide vaccine, and immunogenicity and safety of second and third doses in older adults. *Hum Vaccin* 2011; 7: 919–928.
31. Lazarus R, Clutterbuck E, Yu LM, *et al.* A randomized study comparing combined pneumococcal conjugate and polysaccharide vaccination schedules in adults. *Clin Infect Dis* 2011; 52: 736–742.
32. Pilishvili T, Lexau C, Farley MM, *et al.* Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis* 2010; 201: 32–41.
33. Leal J, Vanderkooi OG, Church DL, *et al.* Eradication of invasive pneumococcal disease due to the seven-valent pneumococcal conjugate vaccine serotypes in Calgary, Alberta. *Pediatr Infect Dis J* 2012; 31: e169–175.
34. Jorgensen JH, Doern GV, Maher LA, *et al.* Antimicrobial resistance among respiratory isolates of *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* in the United States. *Antimicrob Agents Chemother* 1990; 34: 2075–2080.
35. Spika JS, Facklam RR, Plikaytis BD, *et al.* Antimicrobial resistance of *Streptococcus pneumoniae* in the United States, 1979–1987. The Pneumococcal Surveillance Working Group. *J Infect Dis* 1991; 163: 1273–1278.
36. Doern GV, Heilmann KP, Huynh HK, *et al.* Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the United States during 1999–2000, including a comparison of resistance rates since 1994–1995. *Antimicrob Agents Chemother* 2001; 45: 1721–1729.
37. Jenkins SG, Brown SD, Farrell DJ. Trends in antibacterial resistance among *Streptococcus pneumoniae* isolated in the USA: update from PROTEKT US Years 1–4. *Ann Clin Microbiol Antimicrob* 2008; 7: 1.
38. Klugman KP. The successful clone: the vector of dissemination of resistance in *Streptococcus pneumoniae. J Antimicrob Chemother* 2002; 50: Suppl. S2, 1–5.
39. Rudolf D, Michaylov N, van der Linden M, *et al.* International pneumococcal clones match or exceed the fitness of other strains despite the accumulation of antibiotic resistance. *Antimicrob Agents Chemother* 2011; 55: 4915–4917.
40. Moore MR, Gertz RE Jr, Woodbury RL, *et al.* Population snapshot of emergent *Streptococcus pneumoniae* serotype 19A in the United States, 2005. *J Infect Dis* 2008; 197: 1016–1027.
41. Pletz MW, Shergill AP, McGee L, *et al.* Prevalence of first-step mutants among levofloxacin-susceptible invasive isolates of *Streptococcus pneumoniae* in the United States. *Antimicrob Agents Chemother* 2006; 50: 1561–1563.

42. Pletz MW, McGee L, Jorgensen J, *et al.* Levofloxacin-resistant invasive *Streptococcus pneumoniae* in the United States: evidence for clonal spread and the impact of conjugate pneumococcal vaccine. *Antimicrob Agents Chemother* 2004; 48: 3491–3497.
43. Plessis M, Smith AM, Klugman KP. Detection of penicillin resistance in *Streptococcus pneumoniae* by a seminested PCR strategy. *Methods Mol Med* 2001; 48: 65–75.
44. Stephens DS, Zughaier SM, Whitney CG, *et al.* Incidence of macrolide resistance in *Streptococcus pneumoniae* after introduction of the pneumococcal conjugate vaccine: population-based assessment. *Lancet* 2005; 365: 855–863.
45. Imohl M, Reinert RR, Mutscher C, *et al.* Macrolide susceptibility and serotype specific macrolide resistance of invasive isolates of *Streptococcus pneumoniae* in Germany from 1992 to 2008. *BMC Microbiol* 2010; 10: 299.
46. Wierzbowski AK, Karlowsky JA, Adam HJ, *et al.* Evolution and molecular characterization of macrolide-resistant *Streptococcus pneumoniae* in Canada between 1998 and 2008. *J Antimicrob Chemother* 2014; 69: 59-66.
47. Link-Gelles R, Taylor T, Moore MR, *et al.* Forecasting invasive pneumococcal disease trends after the introduction of 13-valent pneumococcal conjugate vaccine in the United States, 2010–2020. *Vaccine* 2013; 31: 2572–2577.
48. Truck J, Lazarus R, Jonsdottir I, *et al.* Pneumococcal polysaccharide vaccine efficacy and routine use of conjugate vaccines in infants: there is no need for a vaccine program in older adults at present. *Clin Infect Dis* 2012; 55: 1577–1579.
49. Mann B, Thornton J, Heath R, *et al.* Broadly protective protein-based pneumococcal vaccine comprised of pneumolysin toxoid–CbpA peptide recombinant fusion protein. *J Infect Dis* 2013 [In press DOI: 10.1093/infdis/jit502].
50. Schulz C, Hammerschmidt S. Exploitation of physiology and metabolomics to identify pneumococcal vaccine candidates. *Expert Rev Vaccines* 2013; 12: 1061–1075.
51. Hak E, Grobbee DE, Sanders EA, *et al.* Rationale and design of CAPITA: a RCT of 13-valent conjugated pneumococcal vaccine efficacy among older adults. *Neth J Med* 2008; 66: 378–383.
52. Moberley S, Holden J, Tatham DP, *et al.* Vaccines for preventing pneumococcal infection in adults. *Cochrane Database Syst Rev* 2013; 1: CD000422.
53. Huss A, Scott P, Stuck AE, *et al.* Efficacy of pneumococcal vaccination in adults: a meta-analysis. *CMAJ* 2009; 180: 48–58.
54. Maruyama T, Taguchi O, Niederman MS, *et al.* Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomised and placebo controlled trial. *BMJ* 2010; 340: c1004.
55. Prymula R, Peeters P, Chrobok V, *et al.* Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both Streptococcus pneumoniae and non-typable *Haemophilus influenzae*: a randomised double-blind efficacy study. *Lancet* 2006; 367: 740–748.
56. Klugman KP, Madhi SA, Huebner RE, *et al.* A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med* 2003; 349: 1341–1348.
57. French N, Gordon SB, Mwalukomo T, *et al.* A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults. *N Engl J Med* 2010; 362: 812–822.
58. French N, Nakiyingi J, Carpenter LM, *et al.* 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet* 2000; 355: 2106–2111.
59. Stoehr GA, Rose MA, Eber SW, *et al.* Immunogenicity of sequential pneumococcal vaccination in subjects splenectomised for hereditary spherocytosis. *Br J Haematol* 2006; 132: 788–790.
60. Russell FM, Licciardi PV, Balloch A, *et al.* Safety and immunogenicity of the 23-valent pneumococcal polysaccharide vaccine at 12 months of age, following one, two, or three doses of the 7-valent pneumococcal conjugate vaccine in infancy. *Vaccine* 2010; 28: 3086–3094.
61. Abzug MJ, Pelton SI, Song LY, *et al.* Immunogenicity, safety, and predictors of response after a pneumococcal conjugate and pneumococcal polysaccharide vaccine series in human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. *Pediatr Infect Dis J* 2006; 25: 920–929.
62. Rose MA, Schubert R, Strnad N, *et al.* Priming of immunological memory by pneumococcal conjugate vaccine in children unresponsive to 23-valent polysaccharide pneumococcal vaccine. *Clin Diagn Lab Immunol* 2005; 12: 1216–1222.
63. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Am J Transplant* 2013; 13: 232–235.
64. Drake JW. Rates of spontaneous mutation among RNA viruses. *Proc Natl Acad Sci USA* 1993; 90: 4171–4175.
65. Mertz D, Kim TH, Johnstone J, *et al.* Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. *BMJ* 2013; 347: f5061.
66. World Health Organization. Influenza: vaccine use. www.who.int/influenza/vaccines/use/en/ Date last updated: 2013.
67. Centers for Disease Control and Prevention. Persons at Risk for Medical Complications Due to Influenza. www.cdc.gov/flu/professionals/acip/2013-summary-recommendations.htm#at-risk Date last update: August 20, 2013.

68. Reichert TA, Sugaya N, Fedson DS, *et al.* The Japanese experience with vaccinating schoolchildren against influenza. *N Engl J Med* 2001; 344: 889–896.
69. Wolfe RM. Update on adult immunizations. *J Am Board Fam Med* 2012; 25: 496–510.
70. Rebmann T, Zelicoff A. Vaccination against influenza: role and limitations in pandemic intervention plans. *Expert Rev Vaccines* 2012; 11: 1009–1019.
71. Rhorer J, Ambrose CS, Dickinson S, *et al.* Efficacy of live attenuated influenza vaccine in children: a meta-analysis of nine randomized clinical trials. *Vaccine* 2009; 27: 1101–1110.
72. Monto AS, Ohmit SE, Petrie JG, *et al.* Comparative efficacy of inactivated and live attenuated influenza vaccines. *N Engl J Med* 2009; 361: 1260–1267.
73. Kanegae Y, Sugita S, Endo A, *et al.* Evolutionary pattern of the hemagglutinin gene of influenza B viruses isolated in Japan: cocirculating lineages in the same epidemic season. *J Virol* 1990; 64: 2860–2865.
74. Lo YC, Chuang JH, Kuo HW, *et al.* Surveillance and vaccine effectiveness of an influenza epidemic predominated by vaccine-mismatched influenza B/Yamagata-lineage viruses in Taiwan, 2011–12 season. *PLoS One* 2013; 8: e58222.
75. Kieninger D, Sheldon E, Lin WY, *et al.* Immunogenicity, reactogenicity and safety of an inactivated quadrivalent influenza vaccine candidate *versus* inactivated trivalent influenza vaccine: a phase III, randomized trial in adults aged $\geqslant$18 years. *BMC Infect Dis* 2013; 13: 343.
76. Domachowske JB, Pankow-Culot H, Bautista M, *et al.* A randomized trial of candidate inactivated quadrivalent influenza vaccine *versus* trivalent influenza vaccines in children aged 3–17 years. *J Infect Dis* 2013; 207: 1878–1887.
77. Reed C, Meltzer MI, Finelli L, *et al.* Public health impact of including two lineages of influenza B in a quadrivalent seasonal influenza vaccine. *Vaccine* 2012; 30: 1993–1998.
78. Centers for Disease Control and Prevention. CDC advisory committee recommends an influenza vaccine option for persons with egg allergy. www.cdc.gov/media/releases/2013/a0620-FluBlok.html Date last updated: June 21, 2013.
79. Zimmerman RK, Lin CJ, Ross T, *et al.* Randomized clinical trial of high-dose influenza vaccine in nursing home residents. https://idsa.confex.com/idsa/2013/webprogram/Paper43076.html
80. Ansaldi F, Canepa P, Ceravolo A, *et al.* Intanza® 15 mcg intradermal influenza vaccine elicits cross-reactive antibody responses against heterologous A(H3N2) influenza viruses. *Vaccine* 2012; 30: 2908–2913.
81. Young F, Marra F. A systematic review of intradermal influenza vaccines. *Vaccine* 2011; 29: 8788-8801.
82. Baldo V, Baldovin T, Pellegrini M, *et al.* Immunogenicity of three different influenza vaccines against homologous and heterologous strains in nursing home elderly residents. *Clin Dev Immunol*, 2010: 517198.
83. de Roux A, Marx A, Burkhardt O, *et al.* Impact of corticosteroids on the immune response to a MF59-adjuvanted influenza vaccine in elderly COPD-patients. *Vaccine* 2006; 24: 1537–1542.
84. Cheuk DK, Chiang AK, Lee TL, *et al.* Vaccines for prophylaxis of viral infections in patients with hematological malignancies. *Cochrane Database Syst Rev* 2011; 3: CD006505.
85. Eckerle I, Rosenberger KD, Zwahlen M, *et al.* Serologic vaccination response after solid organ transplantation: a systematic review. *PLoS One* 2013; 8: e56974.
86. Beck CR, McKenzie BC, Hashim AB, *et al.* Influenza vaccination for immunocompromised patients: systematic review and meta-analysis from a public health policy perspective. *PLoS One* 2011; 6: e29249.
87. Rivetti D, Jefferson T, Thomas R, *et al.* Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev* 2006; 3: CD004876.
88. Gross PA, Hermogenes AW, Sacks HS, *et al.* The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. *Ann Intern Med* 1995; 123: 518–527.
89. Jefferson T, Rivetti A, Di Pietrantonj C, *et al.* Vaccines for preventing influenza in healthy children. *Cochrane Database Syst Rev* 2012; 8: CD004879.
90. Jefferson T, Di Pietrantonj C, Rivetti A, *et al.* Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev* 2010; 7: CD001269.
91. Tessmer A, Welte T, Schmidt-Ott R, *et al.* Influenza vaccination is associated with reduced severity of community-acquired pneumonia. *Eur Respir J* 2011; 38: 147–153.
92. Avery RK. Influenza vaccines in the setting of solid-organ transplantation: are they safe? *Curr Opin Infect Dis* 2012; 25: 464–468.
93. Touma Z, Gladman DD, Urowitz MB. Vaccination and auto-immune rheumatic diseases: lessons learnt from the 2009 H1N1 influenza virus vaccination campaign. *Curr Opin Rheumatol* 2013; 25: 164–170.
94. Farez MF, Correale J. Immunizations and risk of multiple sclerosis: systematic review and meta-analysis. *J Neurol* 2011; 258: 1197–1206.
95. Fairhead T, Hendren E, Tinckam K, *et al.* Poor seroprotection but allosensitization after adjuvanted pandemic influenza H1N1 vaccine in kidney transplant recipients. *Transpl Infect Dis* 2012; 14: 575–583.
96. Kumar D, Blumberg EA, Danziger-Isakov L, *et al.* Influenza vaccination in the organ transplant recipient: review and summary recommendations. *Am J Transplant* 2011; 11: 2020–2030.
97. Hurst FP, Lee JJ, Jindal RM, *et al.* Outcomes associated with influenza vaccination in the first year after kidney transplantation. *Clin J Am Soc Nephrol* 2011; 6: 1192–1197.
98. Smith AM, Adler FR, Ribeiro RM, *et al.* Kinetics of coinfection with influenza A virus and *Streptococcus pneumoniae*. *PLoS Pathog* 2013; 9: e1003238.
99. Launes C, de-Sevilla MF, Selva L, *et al.* Viral coinfection in children less than five years old with invasive pneumococcal disease. *Pediatr Infect Dis J* 2012; 31: 650–653.

100. Kash JC, Walters KA, Davis AS, *et al.* Lethal synergism of 2009 pandemic H1N1 influenza virus and *Streptococcus pneumoniae* coinfection is associated with loss of murine lung repair responses. *mBio* 2011; 2: e00172–11.
101. McCullers JA, Bartmess KC. Role of neuraminidase in lethal synergism between influenza virus and *Streptococcus pneumoniae*. *J Infect Dis* 2003; 187: 1000–1009.
102. Alicino C, Iudici R, Alberti M, *et al.* The dangerous synergism between influenza and *Streptococcus pneumoniae* and innovative perspectives of vaccine prevention. *J Prev Med Hygiene* 2011; 52: 102–106.
103. Hedlund J, Christenson B, Lundbergh P, *et al.* Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in elderly people: a 1-year follow-up. *Vaccine* 2003; 21: 3906–3911.
104. Christenson B, Lundbergh P, Hedlund J, *et al.* Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study. *Lancet* 2001; 357: 1008–1011.
105. Schwarz TF, Flamaing J, Rumke HC, *et al.* A randomized, double-blind trial to evaluate immunogenicity and safety of 13-valent pneumococcal conjugate vaccine given concomitantly with trivalent influenza vaccine in adults aged $\geqslant$65 years. *Vaccine* 2011; 29: 5195–5202.
106. Ayala-Montiel O, Mascarenas de los Santos C, Garcia-Hernandez D, *et al.* Reactogenicidad de la administración simultanea de las vacunas contra influenza y neumococo en adultos mayores de 55 años de edad [Reactogenicity of the simultaneous administration of influenza and pneumococcal vaccines in adults over 55 years of age]. *Rev Invest Clin* 2004; 56: 27–31.
107. Moffitt KL, Malley R. Next generation pneumococcal vaccines. *Curr Op Immunol* 2011; 23: 407–413.
108. Gamez G, Hammerschmidt S. Combat pneumococcal infections: adhesins as candidates for protein-based vaccine development. *Curr Drug Targets* 2012; 13: 323–337.
109. Talbot HK, Rock MT, Johnson C, *et al.* Immunopotentiation of trivalent influenza vaccine when given with VAX102, a recombinant influenza M2e vaccine fused to the TLR5 ligand flagellin. *PLoS One* 2010; 5: e14442.
110. Atsmon J, Kate-Ilovitz E, Shaikevich D, *et al.* Safety and immunogenicity of multimeric-001–a novel universal influenza vaccine. *J Clin Immunol* 2012; 32: 595–603.

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Educational questions

1. Which one of the following is true? The concept of community-acquired pneumonia (CAP) refers to:
❑ All patients with pneumonia acquired in the community. ❑ All patients with pneumonia acquired in the community and without comorbidity. ❑ All patients with pneumonia acquired in the community and without severe immunosuppression. ❑ All patients with pneumonia acquired outside the hospital.

2. Which one of the following is true? Healthcare-associated pneumonia:
❑ Refers to infections in medical staff that have been acquired in the healthcare system. ❑ Confidently predicts excess mortality due to multidrug-resistant (MDR) pathogens in patients in contact with the healthcare system. ❑ Is a concept that has also been validated in several European countries. ❑ Is not a valid predictor of MDR pathogens in patients in contact with the healthcare system.

3. Which one of the following is true? Nosocomial pneumonia:
❑ Also includes patients with severe immunosuppression. ❑ Excludes early onset pneumonia (this is part of CAP). ❑ Includes early onset pneumonia (pneumonia in patients intubated for ⩽4 days).
❑ Requires broad-spectrum antimicrobial treatment in the presence of risk factors for MDR pathogens; a similar approach should be considered in patients with CAP with a history of hospitalisation and antimicrobial pretreatment within the last 30–90 days.

Continued on next page

4. Which one of the following is false? Pneumonia in the immunosuppressed host:
❑ Includes patients with diabetes, liver cirrhosis and chronic renal failure. ❑ Requires a management approach fundamentally different from CAP and nosocomial pneumonia. ❑ Includes a variety of different types of immunosuppression with different timetables and thresholds for distinct pathogen patterns. ❑ Must also be suspected in patients taking very low steroid dosages (5 mg daily for >2 weeks).

5. Which one of the following is true? Pneumonia in the elderly:
❑ Exhibits a specific pathogen pattern similar to hospital-acquired pneumonia. ❑ Exhibits a specific pathogen pattern only in those residing in a nursing home. ❑ Has specific clinical patterns and increased mortality but not fundamentally different pathogen patterns compared to younger patients. ❑ Refers to patients with immunosuppression due to increasing age.

6. A 52-year-old patient who was previously fit and well is admitted to hospital with CAP. He is not confused and gives a history of 3 days of cough and sputum production. On examination, the blood pressure is 98/60 mmHg, respiratory rate 24 breaths·min^{-1}, pulse rate 120 beats·min^{-1}, temperature 37.5°C and oxygen saturation 85% on air, rising to 95% on 28% oxygen. His laboratory results show a white cell count of 12.1x10^{9} cells·mm^{-3}, C-reactive protein of 155 mg·L^{-1}, sodium 132 mmol·L^{-1}, urea 7.2 mmol·L^{-1}, potassium 4.3 mmol·L^{-1}, albumin 30 g·dL^{-1} and glucose 7.7 mmol·L^{-1}. The arterial pH is 7.41. His chest radiograph shows consolidation in both lower zones with no cardiomegaly. Which of the following statements is false?
❑ The patient has a CURB65 score of 2. ❑ His Pneumonia Severity Index (PSI) score placed him in class II, therefore he can be safely managed as an outpatient. ❑ A measure of oxygen saturations is included in the SMART-COP index. ❑ Based on the IDSA/ATS 2007 guidelines, the patient does not have severe CAP. ❑ Bilateral pneumonia is associated with a higher risk of mortality and intensive care unit (ICU) admission.

7. Which one of the following statements about the CURB65 score is true?
❑ Patients with CURB65 score 4 or 5 should always be managed in an ICU. ❑ CURB65 was originally developed and validated to guide empirical antibiotic selection. ❑ There is no evidence that the CURB65 score can predict 30-day mortality. ❑ The CURB65 severity score can be used in the community because it does not require blood tests. ❑ CURB65 is recommended by both the British Thoracic Society and the IDSA/ATS 2007 guidelines.

8. Which one of the following is true about biomarkers in CAP?
❑ A D-dimer above the reference limit for the healthy population is rare in CAP and indicates a very high likelihood of pulmonary embolism. ❑ A C-reactive protein level that falls by 50% or more from baseline after 3 days is associated with a very good prognosis. ❑ C-reactive protein is superior to procalcitonin for predicting 30-day mortality. ❑ C-reactive protein is normally produced by the liver but is also synthesised by heart and vascular endothelium during inflammation. ❑ Copeptin is a marker of cardiac dysfunction and can predict cardiovascular complications as well as ICU admission.

9. A 77-year-old female is admitted to hospital with a 2-day history of cough and shortness of breath. She is a resident in a nursing home and has a history of breast cancer and Parkinson's disease. On examination she has a blood pressure of 87/52 mmHg after initial fluid resuscitation, respiratory rate 34 breaths·min^{-1}, pulse rate 140 beats·min^{-1}, temperature 38.7°C and oxygen saturation 92% on 60% oxygen. Her laboratory results show a white blood cell count of 2.3x10^{9} cells·mm^{-3}, platelet count 190 cells·mm^{-3}, urea 8.1 mmol·L^{-3}, sodium 129 mmol·L^{-1}, potassium 4.1 mmol·L^{-1} and glucose 8.9 mmol·L^{-1}. Initial antibiotic therapy is commenced with ß-lactam and macrolide combination. Which one of the following criteria would be least likely to influence the decision to admit to the ICU?

❑ Comorbidities and functional status. ❑ Blood pressure following fluid resuscitation. ❑ Hypoxia. ❑ White blood cell count. ❑ Serum glucose.

10. Which one of the following statements about pneumonia-related mortality is true?
❑ The majority of patients dying from pneumonia are admitted to an ICU prior to death. ❑ Mortality in CAP managed in primary care is less than 1%. ❑ Use of the CURB65 or PSI score in clinical practice has been shown to reduce inpatient mortality. ❑ Low albumin is not included in the CURB65 score because it is not associated with increased mortality. ❑ All deaths from pneumonia are preventable with earlier antibiotic therapy and resuscitation in the emergency department.

11. A 60-year-old male is admitted with a right lower lobe pneumonia and haemodynamic instability (blood pressure 82/50 mmHg), and requires admission to the ICU. His CURB65 score is 1, due to the low blood pressure. His hypotension is unresponsive to fluid resuscitation and he is found to have a metabolic acidosis. Which of the following statements is true?
❑ The CURB65 must have been incorrectly calculated, as patients with a CURB65 score of 1 do not require ICU admission. ❑ His individual predicted mortality is 3.2%. ❑ He does not require empirical antibiotic coverage for atypical pathogens. ❑ He meets the IDSA/ATS minor criteria for ICU admission. ❑ The presence of acidosis increases his risk of death, independent of the low blood pressure.

12. Which of the following is not a reason for empirical antimicrobial therapy in CAP?
❑ Lack of sensitivity of microbial tests. ❑ Frequency of antibiotic side-effects. ❑ Lack of rapid results for most microbial tests. ❑ Risk of delaying empirical antibiotic therapy. ❑ Inability to predict microbial cause from presenting features.

13. Which of the following is a reason in favour of dual antibiotic therapy for severe CAP?
❑ Anti-inflammatory effects of ß-lactams. ❑ Dual therapy covers the *in vitro* antimicrobial sensitivity of the common bacterial causes. ❑ Randomised controlled trial results of dual therapy. ❑ High mortality with atypical pathogens. ❑ Side-effect profile of dual therapy.

14. Which one of the following statements about penicillins is true?
❑ They provide good cover for Gram-negative bacteria.
❑ They provide good cover for atypical organisms.
❑ They work by binding to cell wall penicillin-binding proteins. ❑ They work by disruption of bacterial ribosomal function. ❑ They commonly prolong the electrographic QT interval.

15. With respect to empirical antibiotic therapy, which one of the following is not true?
❑ It is recommended by all international guidelines. ❑ Background causative pathogen frequency is essential to make recommendations for empirical therapy. ❑ Background local antimicrobial resistance frequencies are essential to make recommendations for empirical therapy. ❑ Positive microbiological results should guide later antibiotic therapy. ❑ Antibiotic side-effects do not influence empirical therapy recommendations.

16. Which of the following is true with respect to international guidelines for empirical antibiotic recommendations?
❑ They all make the same recommendations. ❑ They are all supported by high-quality research evidence. ❑ Most recommend dual antibiotic therapy for nonsevere CAP. ❑ Most recommend dual antibiotic therapy for severe CAP. ❑ Illness severity is not a factor in empirical recommendations.

Continued on next page

17. Which one of the following is not correlated with a prolonged time to clinical stability?
❑ Compromised baseline status (multiple comorbidities). ❑ Complicated infection. ❑ Concomitant HIV infection. ❑ Infection with resistant pathogens. ❑ High PSI class on admission.

18. Which one of the following has been associated with a positive effect on clinical stability?
❑ Low CURB65 on admission. ❑ Adherence to treatment guidelines. ❑ Low burden of comorbidities. ❑ Young age. ❑ Correct site of treatment.

19. Which of the following is not associated with increased risk of clinical failure?
❑ Multilobar infiltrates. ❑ High PSI class. ❑ Malnourishment. ❑ Elevated procalcitonin on admission. ❑ More than one microbiological isolation.

20. Which of the following is not associated with decreased risk of clinical failure?
❑ Appropriate antimicrobial therapy. ❑ Influenza vaccination. ❑ Initial treatment with fluoroquinolones. ❑ Chronic obstructive pulmonary disease. ❑ Young age.

21. How long does it take to obtain a complete radiographic resolution of pneumonia infiltrates in the majority of CAP patients?
❑ 1–2 weeks. ❑ 2–4 weeks. ❑ 4–8 weeks. ❑ 8–12 weeks. ❑ 24 weeks.

22. Which of the following is not associated with delayed radiographic resolution of pneumonia?
❑ Alcohol abuse. ❑ Smoking history. ❑ Advanced age. ❑ Interstitial infiltrates. ❑ Renal failure.

23. Which of the following best describes the antimicrobial mode of action of macrolides?
❑ Inhibitors of cell wall synthesis. ❑ Inhibitors of protein synthesis. ❑ Inhibitors of nucleic acid synthesis. ❑ Inhibitors of cell membrane function. ❑ All of the above.

24. Which of the following statements are true?
❑ Macrolide treatment in the setting of CAP has been associated with shorter lengths of hospital stay in observational studies. ❑ Macrolide treatment in the setting of CAP has been associated with increased mortality in most observational studies. ❑ Macrolide treatment in the setting of CAP has been associated with decreased mortality in prospective randomised controlled studies. ❑ Macrolide treatment in the setting of hospital-acquired pneumonia has been associated with decreased mortality in prospective randomised controlled studies. ❑ All of the above.

25. Long-term macrolide therapy has been shown to have beneficial effects in:
❑ Chronic obstructive pulmonary disease. ❑ Cystic fibrosis (CF). ❑ Non-CF bronchiectasis. ❑ Diffuse panbronchiolitis. ❑ All of the above.

26. Macrolides may achieve their anti-inflammatory effect through:
❑ Increased production of TNF-α and IL-6. ❑ Decreasing release of pathogen-derived pro-inflammatory proteins due to structurally sound bacterial cell walls. ❑ Increased neutrophil migration to the lungs. ❑ Decreased production of IL-10. ❑ All of the above.

27. Pitfalls of macrolide therapy include:
❑ Cardiovascular toxicity. ❑ Tendon rupture. ❑ Seizures. ❑ Loss of smell. ❑ All of the above.

28. Which of the following statements regarding pneumococcal serotypes is true?
❑ There are 13 serotypes. ❑ There are 23 serotypes. ❑ All serotypes exhibit the same virulence. ❑ Pneumococcal clones can switch their serotype. ❑ Serotypes are distinguished according to membrane proteins.

29. Which of the following statements regarding the pneumococcal polysaccharide vaccine is true?
❑ It induces mucosal immunity. ❑ It induces herd protection effects. ❑ It shows efficacy against invasive pneumococcal disease. ❑ It induces specific memory B-cells. ❑ It induces hyporesponsiveness.

30. Which of the following statements regarding the herd protection effects induced by the pneumococcal conjugate vaccine is false?
❑ It reduces antibiotic resistance in pneumococci. ❑ It protects nonvaccinated adults from invasive pneumococcal disease. ❑ It is accompanied by a shift in serotype spectrum, the so-called "replacement phenomenon". ❑ The main replacement serotype after introduction of PCV7 was 19A, which is now contained in PCV13. ❑ It has resulted in an increase in *Haemophilus influenzae* pneumonias.

31. Which statement regarding influenza and influenza vaccines is false?
❑ Trivalent influenza vaccines contain 2xA and 1xB influenza strains. ❑ Quadrivalent influenza vaccines contain 2xA, 1xB and 1xC influenza strains. ❑ Vaccination of children can reduce influenza-related mortality in older adults. ❑ A live attenuated influenza vaccine for use in children is available. ❑ Influenza C is a very rare cause of human disease.

32. Which statement regarding influenza-related secondary bacterial pneumonia is false?
❑ The synergism between influenza and pneumococcus has been confirmed in animal studies. ❑ Secondary bacterial pneumonia has a higher mortality than primary (nonpandemic) influenza pneumonia. ❑ Epidemiological studies have confirmed the synergistic effect of combined influenza and pneumococcal vaccines. ❑ Pneumococcal conjugate vaccine and influenza vaccine must not be administered concomitantly. ❑ Pneumococcal polysaccharide vaccine and influenza vaccine can be administered concomitantly.

33. Which of the following statements regarding the influenza vaccine is true?
❑ Asthma is not a contraindication for the live attenuated vaccine. ❑ Strategies to improve immunogenicity in the elderly comprise adjuvants and increased dosages. ❑ There is no evidence regarding protection from pneumonia in nursing home residents. ❑ Vaccine efficacy is usually calculated with respect to the protection from laboratory-confirmed influenza. ❑ Influenza vaccine is contraindicated in solid organ transplant recipients to prevent rejection.

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